NSG-622

Neurosciences Research Program

Bulletin

Volume 4, Number 1 Published May 31, 1966

CONTENTS

SLEEP, WAKEFULNESS, DREAMS
AND MEMORY

A report of an NRP Work Session chaired by

Walle J.H. Nauta

and

Werner P. Koella

BLANK PAGE

N E U R O S C I E N C E S R E S E A R C H P R O G R A M
280 Newton Street, Brookline, Massachusetts 02146
Telephone: Area Code 617, 522-6700; Cable: NEUROCENT

SPONSORSHIP AND SUPPORT

The Neurosciences Research Program, sponsored by the Massachusetts Institute of Technology, is an interdisciplinary, interuniversity organization the primary goal of which is to facilitate the investigation of the physical basis of mental processes including memory and learning. To this end the NRP, as one of its activities, conducts scientific meetings to explore crucial problems in the neurosciences and publishes the results of these Work Sessions in this Bulletin. NRP is supported in part by National Institutes of Health Grant No. GM 10211-04, National Aeronautics and Space Administration Grant No. Nsg 462 Amendment 2, Office of Naval Research Grant Nonr(G)-00067-65, The Rogosin Foundation and Neurosciences Research Foundation, Inc.

SLEEP, WAKEFULNESS, DREAMS AND MEMORY

A Report of an NRP Work Session
held January 30-31, 1965

by

*Walle J.H. Nauta
Massachusetts Institute of Technology, Cambridge, Mass.
*Werner P. Koella
Worcester Foundation for Experimental Biology, Shrewsbury, Mass.
Gardner C. Quarton
Neurosciences Research Program, Brookline, Mass.

CONTENTS

* Cochairmen (Staff Editor: Anne H. Rosenfeld)

LIST OF PARTICIPANTS

Karl M. Dallenbach
Department of Psychology
University of Texas
Austin, Texas

William C. Dement
Department of Psychiatry
Stanford University
Palo Alto, California

Edward V. Evarts
Laboratory of Clinical Science
National Institute of Mental Health
Bethesda, Maryland

Franz Halberg
Department of Pathology
University of Minnesota
Minneapolis, Minnesota

Raul Hernández-Peón
Instituto de Investigaciones Cerebrales, A.C.
Moras 445
Mexico 12, D.F., Mexico

Rudolf Hess
E.E.G. Department
Kantonsspital, Ramistr. 100
8006 Zurich, Switzerland

Murray Jarvik
Department of Pharmacology
Albert Einstein College of Medicine of Yeshiva University
Bronx, New York

Michael Jouvet
Department of Experimental Medicine
University of Lyon
Lyon, France

Seymour S. Kety
Laboratory of Clinical Science
National Institute of Mental Health
Bethesda, Maryland

Nathaniel Kleitman
222 Washington Avenue
Santa Monica, California

Werner P. Koella
Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

Walle J. H. Nauta
Department of Psychology
Massachusetts Institute of Technology
Cambridge, Massachusetts

Ian Oswald
Department of Psychiatry
University of Western Australia
Victor Square
Perth, Western Australia

Gian Franco Rossi
Clinica Neurochirugica e Clinica Delle Malattie Nervos e Mentali
Universita de Genoa
Genoa, Italy

Vernon Rowland
Department of Psychiatry
Western Reserve University
University Hospital
Cleveland, Ohio

Francis O. Schmitt
Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts

Harold L. Williams
Department of Psychiatry, Neurology and Behavioral Sciences
University of Oklahoma
Oklahoma City, Oklahoma

BLANK PAGE

INTRODUCTION

The NRP Work Session on "Sleep, Wakefulness, Dreams and Memory" was held on January 30 and 31, 1965 at the NRP Center in Brookline, Massachusetts. Drs. Werner P. Koella and Walle J. H. Nauta served as cochairmen.

The choice of the topic "Sleep, Wakefulness, Dreams and Memory" as the subject of an NRP Work Session reflects the orientation of the Associates' interest toward fundamental biological phenomena. Detailed studies of the daily activity cycle so far have been restricted to a limited number of animal species. Nevertheless it is likely from all appearances that virtually all vertebrate classes at least are subject to a diurnal rhythm in behavioral activity and responsiveness. This rhythm, although influenced by external environmental factors, is not determined by such factors, and thus appears to manifest a mechanism of intrinsic program control.

Despite several decades of intensive multidisciplinary study, determining mechanisms of the sleep-wakefulness cycle have remained elusive. During the last 15 years, however, remarkable progress has been made in the analysis of the phenomenon of sleep, especially as it manifests itself in changes of central neural activity and its attendant perceptual, ideational and behavioral states. The Work Session here reported was intended to provide a survey of the contemporary status of the problem.

The writer who attempts to describe a phenomenon as fundamental and encompassing as the sleep-wakefulness cycle finds himself confronted with a formidable challenge. For the sake of a readable account, he is compelled to organize his material in some or other form unavoidably expressing his interpretation of the causal sequence; yet any such classification must remain tentative as long as the ultimate causative mechanism of the diurnal cycle remains unknown. It is therefore necessary to interpret such terms as: "mechanisms of sleep induction," "central regulatory mechanisms," etc., used in the present account, with appropriate reservations. They convey no more than a reasonable certainty that the major behavioral aspects of sleep have certain consistently identifiable central nervous corollaries. Research in sleep has only begun to reach beyond this causative level, and much further study will be needed to expose the next deeper biological substratum.

I. OVERVIEW

Sleep is usually defined phenomenologically as a reversible, periodically occurring state of reduced muscular activity and sensory reactivity of an organism to the surrounding world. Our phenomenological knowledge is quite advanced about the various functional changes that distinguish sleep from wakefulness (and from other states characterized by a loss of wakefulness). Little, however, is known about the function of sleep. Despite some anecdotal evidence suggesting that sleep serves to restitute, to "de-tire," or to refill some well of energy depleted during wakefulness, virtually nothing is known about the processes underlying that depletion and restitution. Similarly, virtually nothing is known about how and where sleep-inducing stimuli act, although there is some evidence that tiredness is the subjective manifestation of a buildup of a hypnogenic factor, that an internal clock is involved in timing the onset and termination of sleep, and that the reduction of sleep-disturbing stimuli such as light, noise, muscular activity and nociceptive signals, facilitate the onset and continuance of sleep. Finally, little is known about the organizational control of sleep. Indeed, there is still some controversy whether any controlling, integrating or organizing apparatus must be postulated. Some investigators, such as Kleitman, view sleep as a mere letdown phenomenon, and claim the "various concomitants and characteristics of sleep can all (with the notable exception of the positive Babinski response and certain types of electroencephalographic patterns) be obtained in a waking subject under certain conditions of horizontal body position, rest and muscular relaxation."

Other (and probably the majority of) investigators point out that the shift from the waking to the sleeping state involves distinctive physiological changes characteristic of sleep alone, and that these changes are not the result of a mere "letdown"; in fact, a number of bodily functions and single functional units are, if anything, more active in sleep than in waking. New evidence presented by many of the participants in this Work Session, as well as older observations that sleep can be induced experimentally by electrical (or chemical) stimulation of various brain parts, adds further strength to the view that sleep is an actively induced and controlled phenomenon.

What, then, distinguishes sleep from wakefulness somewhat more specifically than is indicated in the preceding

discussion? There are, indeed, a great many sleep "symptoms" encompassing functional changes in a large variety of bodily activities and manifest in such indicators as the pupil size, blood pressure, skeletal muscle contraction, reactivity to sensory stimuli, and EEG characteristics. The latter, while not the most obvious of the "sleep indicators," have been very valuable and instrumental in studies of sleep. Soon after discovery of the EEG by Berger, it became obvious that with the transition from restful waking to sleep, a number of fundamental changes occurred in the brain's electrical pattern, characterized by a general slowing of the more-or-less regular waves and the appearance of "spindles." Based mostly on measurements of the arousal threshold, Loomis, et al.(1) were able to establish a scale of five sleep stages ("A" through "E") each characterized by unique EEG patterns indicative of a particular "level" of sleep (Fig. 1). This scale is still very much in use, although attempts have been made to simplify or complicate it, either by consolidation of two or more of Loomis' stages, or by the addition of substages. Of the newer classifications, the one by Dement and Kleitman (1957a) has also been widely accepted, at least in part because it includes a new "phase" of sleep, detected during the last ten or so years, the so-called paradoxical, desynchronized, fast-wave, low-voltage, REM, or activated sleep. (See Fig. 2.) Dement (1958), and Dement and Kleitman (1957b) (who were the first to give a full description of the phase) observed that in man as well as in experimental animals the EEG suddenly may change from the slow-wave-and-spindle pattern to a fast-wave low-voltage tracing resembling the activation pattern of the aroused waking organism; the subjects otherwise exhibit all the signs of sleep, such as narrow pupils, relaxation of the nictitating membrane (in cats), low reactivity to sensory stimuli, and relative rest of the body (though twitching of the limbs often accompanies this fast-wave sleep). Typically, these phases, which usually occur in man after an initial slow phase of sleep lasting about 60 minutes, are always accompanied by rapid eye movements (REM's). Furthermore, the high incidence of dream recall in subjects awakened during REM sleep, and the low incidence of dream recall in those awakened during slow-wave (i.e., orthodox or deep) sleep, led to the assumption that dreaming occurs, mainly, during paradoxical sleep. More will be said about these more psychological aspects of sleep later in this report. (See pages 50-69.)

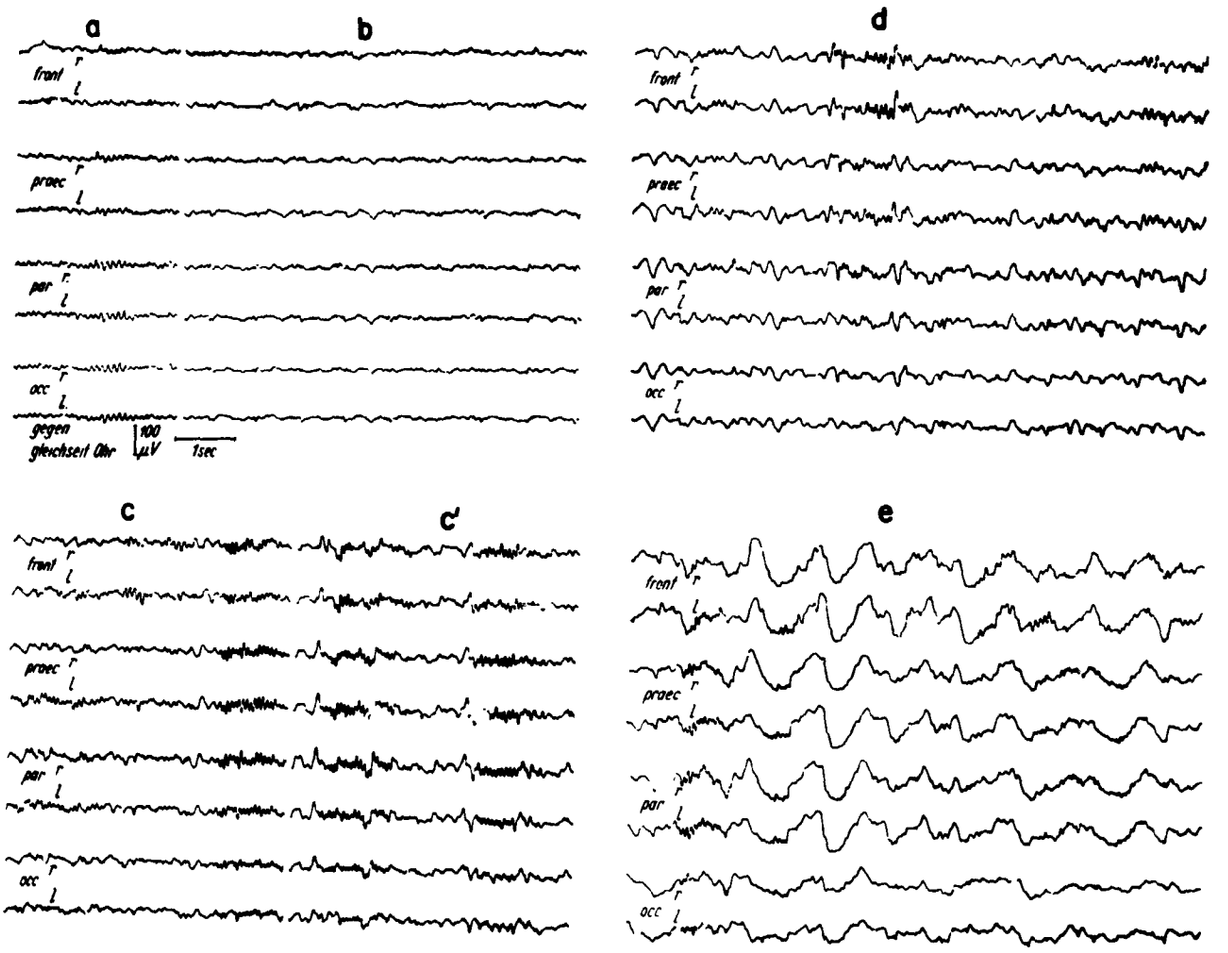

Figure 1. The EEG stages in a 29-year-old healthy man. Eight channels recorded in monopolar arrangement as indicated, against ear lobe. a:waking with alpha waves; b:floating or B-stage; c:C-stage with spindles and increasing amount of delta waves(c'); d:D-stage with larger delta waves (3/sec); e:E-stage, large, very slow deltas (0.6-1/sec). [From: Jung, R. (1953): Neurophysiologische Untersuchungsmethoden, Handbuch der innern Medizin, Bd. V/1, s.1206-1420 Berlin: Springer.]

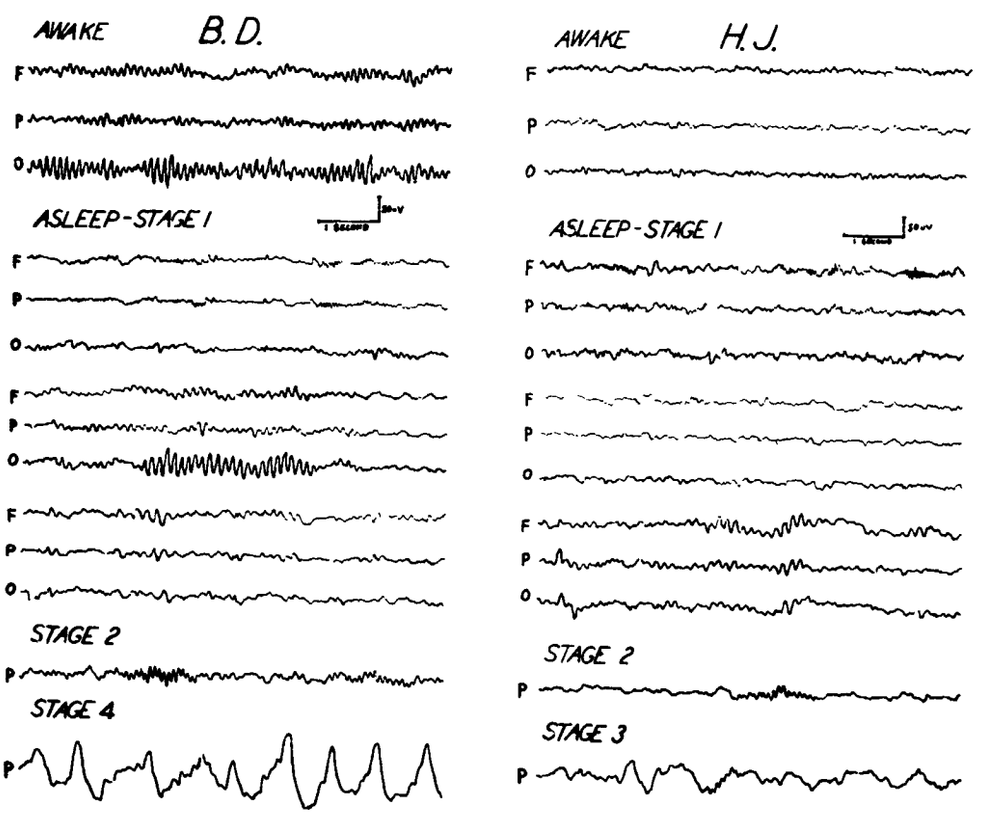

Figure 2. EEG samples from two subjects to illustrate the Dement-Kleitman classification of sleep patterns and some of the variations in the stage 1 category associated with rapid eye movements. In the waking and stage 1 samples, each group of three tracings, F-frontal, P-parietal, O-occipital, is simultaneous. All samples were taken from one night's recordings. [From: Dement, W. and Kleitman, N. (1957): Electroenceph. Clin. Neurophys. 9:679.]

II. PHYSIOLOGICAL PHENOMENOLOGY OF SLEEP

A. Functional Differences Between Wakefulness and Sleep: N. Kleitman

Called upon to describe some of the functional differences between wakefulness and sleep, Dr. Kleitman* first pointed out that the important question is not so much, What is sleep?, but rather, What is wakefulness? He emphasized that sleep is a relatively simple state; we fall asleep at the end of a certain number of hours of wakefulness. Sleep, Kleitman said, looks from the outside like a lifeless condition which we have come to think of as a form of mild anesthesia or coma. Despite the presence of new information indicating some auxiliary active participation of certain parts of the nervous system, Kleitman views sleep as a passive state; it is nothing more than a diastole, or the rest of the organism; and by rest is meant, particularly, a rest of the body musculature.

The muscular system, in Kleitman's opinion, plays an important role in maintaining wakefulness and producing the "necessity of sleep." He views muscular inactivity as one of the functional differences that distinguishes sleep from wakefulness. Since the sleep-waking cycle is not markedly altered in human quadriplegics, one may assume that small muscles about the head and face play an important role. Indeed, the eye muscles have an extremely large cerebral cortical representation; thus, it seems that the "cortical" importance of muscular systems determines the role played in the sleep-waking cycle. During waking, even when one is completely relaxed or even sick and immobilized, there is still a great deal of muscle tonus, which creates fatigue. Muscular fatigue, then, a discomfort perhaps from pain receptors, makes one stop activity and helps to induce sleep. Perhaps the "stopping" per se is effective as a hypnogenic factor.

During sleep an abundance of signals still "come in," and a great deal of internal (i.e., central nervous) reverberation takes place, but "very little, if anything goes out." Some sort of block must occur during sleep (see also

---

* It seems noteworthy to mention at the outset of this presentation that Kleitman has written a most outstanding book on sleep (1939), which recently appeared in a revised edition. With this classical work Kleitman has established himself as the dean of the American sleep investigators. (W.P.K.)

Dr. Evarts' report, pp. 15-23) that is a fundamental feature of the sleeping phase. Another manifestation of this block is the appearance during sleep of a positive Babinski sign (i.e., a dorsal extension of the big toe in response to tactile stimulation of the sole of the foot), which is ordinarily related to lesions in the pyramidal system.

Still another expression of a cutoff of the periphery from the central motor structures can be seen, according to Kleitman, in Gibbs'[2] observation that when epileptics sleep, epileptic grand mal seizures may well be seen as the typical electroencephalographic patterns, but not convulsions; whereas such patients, when awakened, promptly show a full-blown epileptic attack with muscular involvement.

Another interesting feature of sleep phenomenology is the occurrence of sleepwalking, which had always been thought to be an acting out or "working out" of dreams. Recent experiments have shown, however, that sleepwalking always occurs during stages III and IV (deep, slow-wave sleep), in which little dreaming occurs, in contrast to stage I, REM, during which most dreaming seems to take place. Thus, sleepwalking is probably not related to dreams.

Kleitman proceeded then to describe a number of indicators of 24-hour cycles. Body temperature, for instance, follows a fairly regular 24-hour cycle with a maximum or plateau between noon and 8 p.m.. Individual irregularities in curves may be the manifestations of short-term rest-activity cycles with periods of about 90 minutes. Kleitman believes the large 24-hour cycles are established by individual experience. Thus, changing to a different routine, i.e., 18, 21, or 28 hours, one can establish an 18-, 21-, or 28-hour temperature curve. In sleep-deprived individuals, the 24-hour rhythms persist, and are paralleled by changes in degree of sleepiness as well as by variations in performance, for example in psychomotor and arithmetical tests.

An important feature of the relative stability of the rhythms is well demonstrated if one compares the 24-hour rhythm of temperature and the rhythm of heart rate. In normal 24-hour day-activity, night-sleep patterns, temperature and heart-rate variations run nicely parallel. If one changes to an 18-hour day or reverts to night shifts, the heart-rate variations immediately follow the new routine, whereas temperature has a tendency to adhere to the old 24-hour routine. In Kleitman's view, drop in heart rate is simply a concomitant

of lying down and resting, whereas the temperature cycle is an acquired, precisely adjusted rhythm with a certain degree of stability.

Dr. Halberg, an expert on circadian rhythms, pointed out that there are indeed differences between the behavior, say, of circadian rhythms in body temperature, on the one hand, and of heart rate, on the other hand. Thus, when human beings are cut off from time cues for several months the amplitude of the circadian rhythm in heart rate might decrease, while that of the body-temperature rhythm might not. He stressed, however, that under such critical conditions the circadian rhythm in heart rate nevertheless persists. Furthermore, Dr. Howard Levine, using the spectral analytic technique has detected a circadian component even in the heart rate of a child in prolonged coma (unpublished).

Kleitman finally also mentioned a number of important facts about blood gases. Both CO_2 tension in the blood and CO_2 partial pressure in the alveoli of the lungs are raised during sleep, indicating a drop in irritability of the CO_2-sensitive part of the respiratory center. Narcoleptics, however, have as high a CO_2 pressure during wakefulness as normal subjects have during sleep, indicating that such patients are (at least according to their blood gases) not fully awake. In a sense, the CO_2 pressure, according to Kleitman, is an indicator of vigilance; it is low during waking and high during sleep.

B. Stages of Sleep According to the EEG: R. Hess

Dr. Hess dedicated part of his presentation to a review of the electroencephalographic signs of sleep, (Fig. 3) and then discussed some of his own findings and "the meaning of the EEG changes with respect to brain function." In his review, Hess pointed to some limitations in the classification of the various EEG stages, in particular, the rapid shifts from one stage to the other that may make identification of a given sleep stage rather difficult. In addition, he noted that the "classical" sleep stages can be clearly distinguished only in younger persons, whereas in older subjects, newborn babies and infants, deviations from the classical scheme are encountered. (Even in younger adults EEG patterns may occur during sleep that do not fit any of the classical stages.) Finally, Hess pointed to the lessened degree of correlation between behavioral indicators and EEG signs in the later phases of sleep. Regarding paradoxical sleep characteristics, Hess

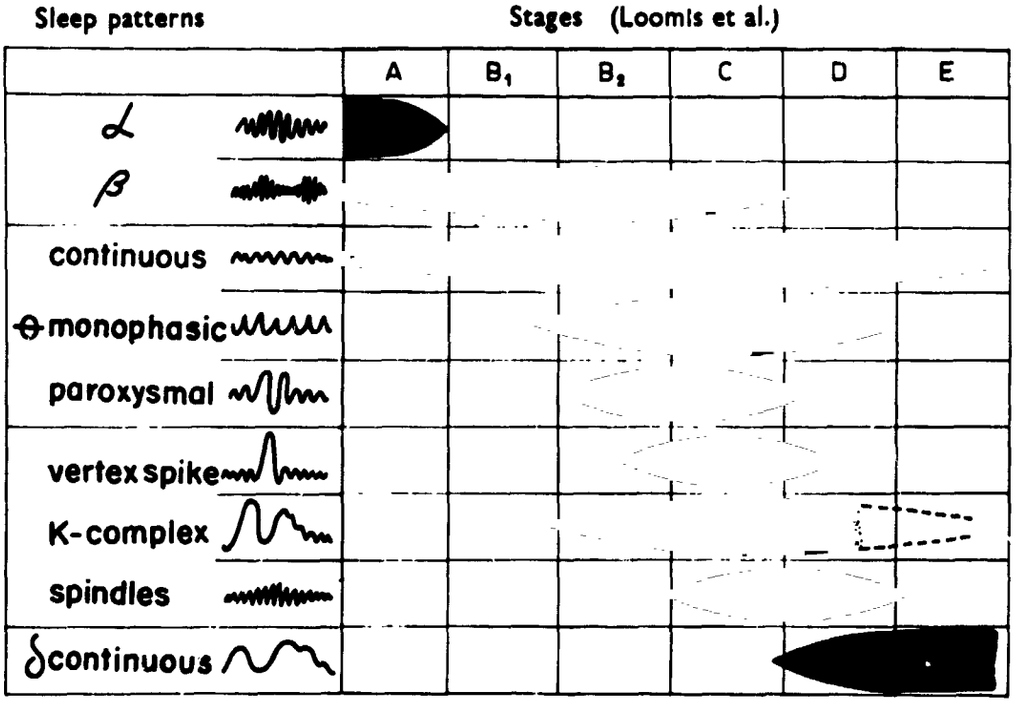

Figure 3. Schematic representation of several sleep patterns and their constituents, as they occur in the (Loomis) stages of sleep. [From: Hess, R.W. (1964): Electroenceph. Clin. Neurophys. 16:44-55.]

mentioned the slightly slowed alpha activity, the low-voltage slow waves (in the so-called theta range, i.e., 4-to-6-per-second waves), and the fair amounts of faster activity which make up the pattern. He also pointed out that the paradoxical sleep pattern in the cat is not identical with the activation pattern of the aroused awake animal.

Hess then proceeded to discuss a number of specific EEG sleep phenomena, namely the "vertex sharp wave," the "K-complex," and the less commonly mentioned "occipital positive spike-like waves." All three are paroxysmal phenomena, the first two usually occurring in response to stimuli. The vertex sharp wave is, as the term indicates, a sharp, often biphasic wave, occurring over the medial aspect of the head; it is most prominent in children and becomes inconspicuous with increasing age. It occurs mostly in the (light) B-stages of sleep, though it is also found that the C-stage (characterized by spindles), and is not rare in the early D-stage. The K-complex, on the other hand, occurs in all age groups; it has a longer duration, higher voltage and a wider spread over the head than the vertex sharp wave, and is most prominent in the C-stage of sleep. Vertex waves generally occur without subsequent changes in the EEG, whereas the K-complex is often followed by a train of alpha-like waves and EEG signs of partial arousal.

The occipital spike-like waves are not, in Hess' view, stimulus-induced and are not identical with lambda waves (random, electropositive, sharp or saw-tooth waves which appear with visual attention), despite their resemblance to them.

Hess mentioned the following relations between sleep stages and eye movements: while awake, vertical blink-like movements are prominent, but often without any change in the alpha waves (which are supposed to indicate that the cortex is in its waking state). With drowsiness and the onset of sleep, these vertical jerks are replaced by slow, regular horizontal movements which, with deepening of sleep, become more irregular, still slower, intermittent, and finally disappear. With every arousal, as well as during episodes of paradoxical sleep, rapid, jerky movements reappear.

In Hess' view, this evolution of eye movements during sleep reflects changes in the functional state of brain stem centers which do not always parallel that of the cortex.

Hess finally offered some theoretical considerations on the various sleep states: "Since in paradoxical sleep the cortex seems to react as in light sleep, and since dreaming and incorporating of exterior stimuli into dreams show a fairly high level of cortical activity while the arousal threshold is high, one might assume that the collaterals of sensory inflow, which lead to the arousal center, are blocked, perhaps by occlusion. The purpose of this state, if you will permit a teleological argument, would be to allow these centers to recover, while protected against disturbance from without. This would be a most dangerous state for any creature, except civilized man in peacetime, unless a subsidiary arousal mechanism were provided by the cortex, which itself passes to a state of near-wakefulness for the period in question, and thus is in a position to screen and assess the significance of incoming messages much better than in slow-wave sleep. In cases of vital importance, the reticular system is aroused by assumedly still functional descending pathways, so that the organism is able to react in an appropriate way.

"In slow-wave sleep, on the other hand, the discriminatory faculty of the cortex may be assumed to be lessened, and the reticular system is in charge of arousing the cortex to some extent for any arriving stimulus, so that its meaning may be assessed. Since the cortex, having an incomparably more complex function than the primitive arousal center, needs rest and recovery in the first place, paradoxical sleep does not occur unless abundant slow-wave sleep has taken place."

C. Electrophysiological Phenomena: Single-Unit Discharges and Evoked Responses: E. Evarts

Microelectrode recordings of the discharges of single neurons in various parts of the brain provide an index of functional differences between sleep and waking that supplements the evidence obtained by the electroencephalographic technique. In recent years, techniques worked out by Jasper[3] and by Hubel[4] have made it possible to record from single units (which can be "held" for several hours) in various stages of vigilance. While earlier findings of the maintenance of cerebral electrical (EEG) activity and the persistence or the enhancement of sensory-evoked potentials during sleep had already indicated the continued presence of nervous activity during sleep, the results of recent recordings of single nerve-cell activity have raised serious questions as to the validity of the notion of "brain sleep"; not only do the nerve cells of numerous brain areas continue to discharge during sleep,

but in many instances they have been found to discharge at higher mean frequencies during sleep than they do during wakefulness. Among the earlier reports, Huttenlocher[5] has recorded discharges from units in the reticular formation of cats with chronically implanted electrodes. He found that the majority of the cells recorded from showed an increase of discharge frequency as the animals shifted from wakefulness to slow-wave and then to fast-wave sleep. These findings are all the more astonishing since one would expect that the part of the brain containing the classical ascending activating system would be quiescent during sleep. It may be noted, however, that the reticular core is also intimately involved in the control of sleep, so that its increased neuronal activity may signal a discharge in a sleep-inducing, ascending inhibitory system, as well as a release phenomenon. Records from the cerebral cortex suggest indeed that such "disinhibition" takes place during sleep. More will be said about such findings later.

Evarts, in his presentation, reviewed mostly his own extensive work in this field over the past several years, with particular emphasis on his most recent findings. Using the techniques of Jasper[3] and Hubel[4] for recording unit activity, he was able to observe the units in various stages of wakefulness (i.e., with and without movements), as well as of sleep (i.e., slow-wave and fast-wave sleep) in cats and monkeys. In all animals, electrodes were implanted to permit recording of the EEG, the activity of the neck and limb muscles, and, in a number of experiments, to stimulate the medullary pyramid so as to allow identification of cortical neurons whose axons descend through the pyramidal tract. An important aspect of Evarts' work is that it demonstrates that it is not enough to observe the overall frequency of discharge of a few neurons in the transition from wakefulness to sleep; rather, the size of the nerve cells, the area recorded from, the pattern of discharge (regular vs. bursts), the type of wakefulness (i.e., active vs. resting), and the type of sleep (slow-wave vs. fast-wave) are all parameters which must be considered to obtain a clear picture of what happens in the various stages of vigilance, even if one observes a relatively homogeneous population, as Evarts has done.

If one records just the mean discharge frequency from units in the visual cortex of cats, a pattern as shown in Fig. 4 emerges: during resting wakefulness and slow-wave sleep, the discharge frequency is relatively low and of about the same magnitude; during active wakefulness (i.e., when the cat

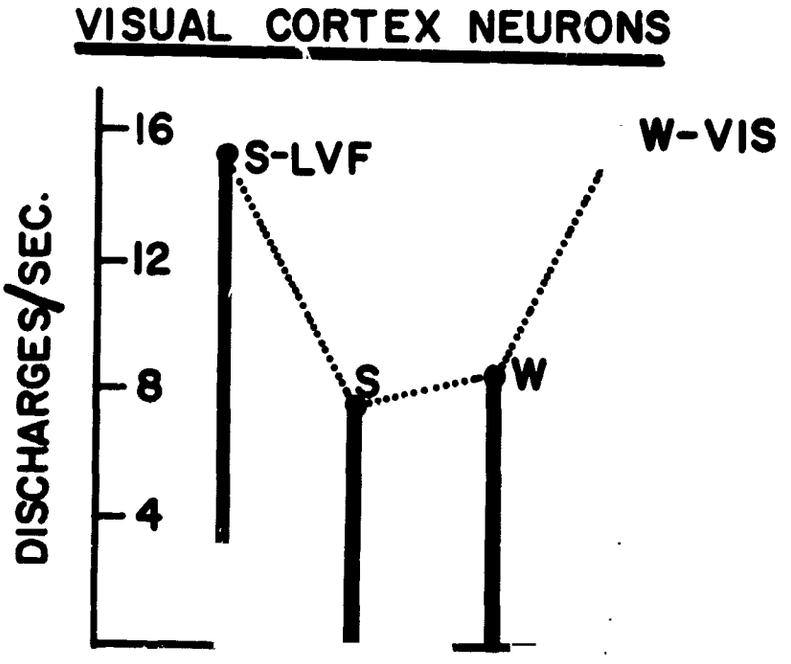

Figure 4. Comparison of discharge frequency of visual cortex neurons during low-voltage, fast-wave sleep (S-LVF), slow-wave sleep (S), resting wakefulness (W), and active wakefulness (W-VIS). [Evarts]

is looking around) as well as during "fast" sleep, the discharge frequency is considerably increased.

Evarts then demonstrated that merely monitoring the overall means of discharge frequency derived from a large number of neurons does not tell the whole story. Closer analysis of the behavior of pyramidal tract neurons (PTN's) from the motor cortex of monkeys, shows that the shift from resting wakefulness to slow-wave sleep actually is paralleled by a massive change in discharge frequency of many individual neurons; during sleep, elements that had been silent during waking begin to discharge, while others that had been tonically and regularly active during waking reduce their discharge rate. "What has happened," said Evarts, "is that the differentiation within the group has fallen away."

There are, furthermore, qualitative changes in the discharge behavior of neurons that are of course overlooked if only the total amount of discharge is recorded. In Fig. 5 a pyramidal neuron from the motor cortex of the monkey is shown during three different conditions: restful waking (W), slow-wave sleep (S), and low-voltage fast-wave sleep (S-LVF). While the overall discharge rate of this neuron stays about the same in W and S-LVF, there is a marked change in discharge characteristics: during resting wakefulness (i.e., no spontaneous movements), the discharge is fairly regular at intervals unlikely to be shorter than 20 msec to 30 msec. During slow-wave sleep the spikes may group themselves into short bursts, whereas during fast-wave sleep, pronounced groups of high-frequency discharges are seen, separated by long intervals. These bursts are very similar to those observed after strychnine treatment of the cortex. Furthermore, they are often associated with small twitches of the extremities.

Evarts proceeded then to talk about evoked responses, particularly the changes in discharge rate and pattern of visual cortex neurons in response to light flashes. It had been known for a long time that evoked responses recorded with gross electrodes commonly become larger during sleep than during wakefulness. Evarts, too, had observed (1961) that there is often an increase in flash-evoked unit discharge during sleep as compared to wakefulness. In more recent work, Evarts found that while there are indeed many units that discharge more intensely to photic stimuli during sleep, others exist that discharge more markedly during waking. This difference is related to the latency of response. Units that are

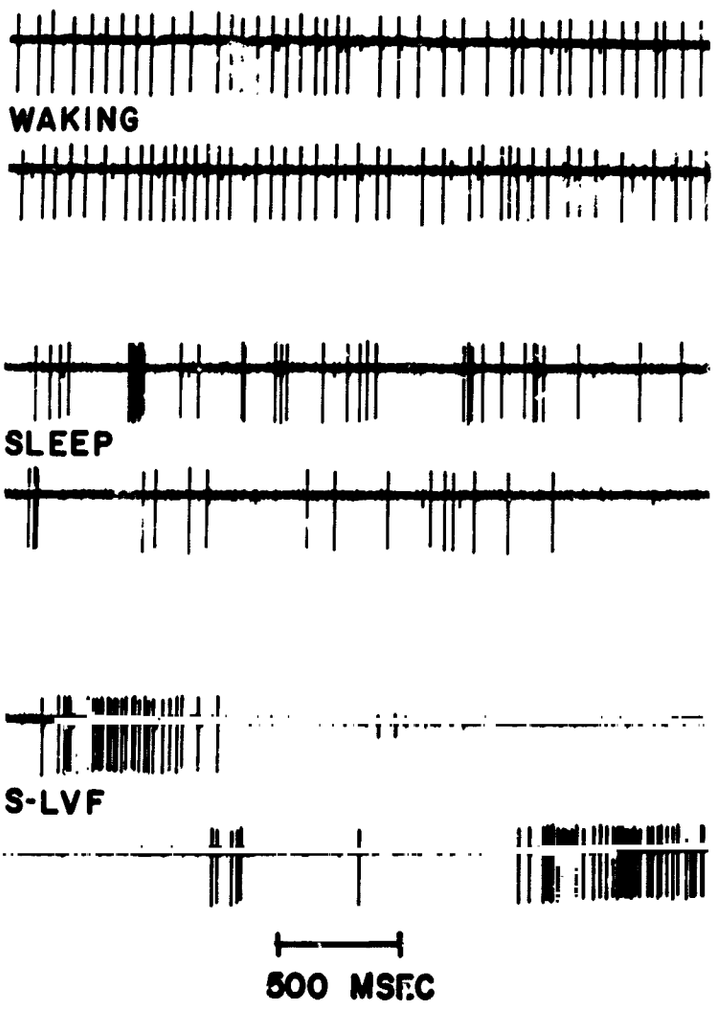

Figure 5. Comparison of discharge patterns of a pyramidal tract neuron from monkey motor cortex during three conditions: restful waking, slow-wave sleep, and low-voltage fast-wave sleep (S-LVF). [Evarts]

more responsive during sleep are those that respond soon after the evoking stimulus, i.e., those with short response latency, whereas, the units that are more responsive during waking are those with long response latency. A unit that responds at short latency and then again at long latency may show an increase in its short-latency response and a decrease in its long-latency response in sleep as compared to waking. The failure of the long-latency response thus appears to result from a failure of arrival of the long-latency input to the unit rather than from inexcitability of the unit.

Continuing his work, Evarts then investigated in greater detail the question of which neurons speed up during sleep, and which slow down to achieve the "de-differentiation" mentioned above. In particular, his concern was whether acceleration or deceleration during sleep depends on the size of the neuron. Evarts obtained information about the sizes of the cells in the motor cortex by means of electrical stimuli delivered to the medullary pyramid which then excited pyramidal tract neurons (PTN's) in the cortex antidromically. From the latency of the antidromically induced response, the conduction velocity of the pyramidal fiber involved could be calculated, and further, the fiber and cell sizes could be inferred. Once Evarts had established the fiber and cell size for all units studied with the microelectrode, he investigated their behavior in various stages of vigilance (Fig. 6). The results of this study can be briefly summarized as follows: The larger (short-latency) neurons are usually silent or hardly active during waking movements and during sleep. The smaller PTN's are continuously active during restful waking, but some of these small PTN's may actually show reduced discharge during movements. During slow-wave sleep the overall firing rate of the smaller PTN's slows down, in marked contrast to the increased discharge frequency of the largest PTN's. With REM sleep, small PTN's have mean discharge frequencies similar to those of the waking state.

In another study, Evarts investigated the discharge behavior of neurons in the motor cortex during wakefulness with and without learned movements of the hand, as well as during various stages of sleep. Often, it was found that in the course of certain movements (i.e., lifting the hand in a conditioned response to a light) two neurons behaved reciprocally; that is, one reduced, while the other increases its firing rate. With the onset of sleep, this differentiation and reciprocal patterning was lost.

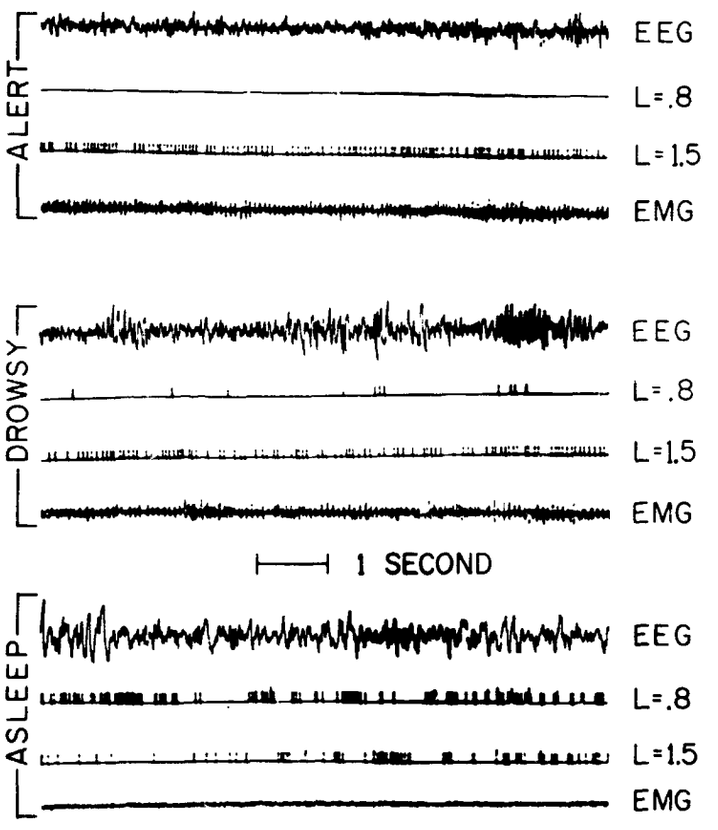

Figure 6. Discharge pattern of a pair of pyramidal neurons (identified by antidromic stimulation) recorded with the same microelectrode. The larger unit (response latency(L) 0.8 msec) was inactive during waking without movements (top set), became somewhat active during drowsiness, and developed bursts during (slow-wave) sleep (bottom). The other smaller unit (latency (L) 1.5 msec) was regularly active during quiet waking, and developed bursts with the onset of sleep. The EMG (electromyogram) was taken from contralateral arm muscles. [From: Evarts, E. (1965): J. Neurophysiol. 28:216-228.]

In Evarts' view, de-differentiation of neuronal discharge is an important aspect of sleep; there seems to be "more entropy," a loss of gradients between adjacent neurons, more positively correlated discharge and, thus, "much less information."

A second important point is that a certain decoupling between the cortical neurons and the periphery appears to take place during sleep. Amazingly, during fast-wave sleep, PTN's may discharge briefly at rates much higher than they do in wakefulness during movement; yet no movements, or only slight ones occur during this sleep stage. Evidently, the pyramidal discharge is disorganized, and is a "meaningless jumble" because the important reciprocal code is lost. Furthermore, sleep is associated with maintained, tonic inhibition of the spinal cord motoneurons. This tonic inhibition "turns off" the periphery, with a consequent alteration of spinal reflexes as well as a reduction in the effectiveness of downward discharges from supraspinal levels.

As to the interpretation of some of his results, Evarts had at first thought that the small neurons that slow down during sleep may actually "need" sleep since, due to their small volume-to-surface ratio, they would "run out" of potassium and take up sodium. But a closer look at the behavior of these smaller PTN's revealed that during slow-wave sleep they still discharge at rates somewhat higher (about 9 per second, on the average) than do the larger PTN's, which speed up from near zero to about 6 to 7 per second in sleep. Thus, sleep does not seem well designed to serve the purpose of restoration alone, since "no matter how you fatigue this system," such restoration could be accomplished within about an hour by complete inactivity during that period.

Finally, Evarts offered some ideas about possible mechanisms responsible for the difference in behavior of cortical neurons during waking and sleep. The fact that during waking cortical neurons tend not to discharge beyond a certain upper frequency limit, may indicate that a certain minimum interspike interval is due to recurrent inhibition similar or analogous to that exerted by the Renshaw cells associated with the spinal motoneurons. In the spinal cord, the action of the Renshaw circuit can be blocked by strychnine, causing the disinhibited motoneurons to discharge at much higher rates. Strychninization of the cortex also shortens the minimum interspike interval; there is now a considerable body of evidence showing that recurrent inhibition does exist in the

cortex. In view of the similarity of the cortical neuron discharge pattern during fast-wave sleep to the strychnine-induced discharge pattern, Evarts' views "this kind of pattern during sleep as (probably being) due to the failure of some (recurrent) inhibitory mechanism." It was speculated that during waking, excitatory impulses arising in subcortical regions might keep the cortical analog of the Renshaw cell active and provide inhibition of the cortical pyramidal neurons; fading of the ascending, facilitatory discharge during sleep would de-facilitate the cortical "Renshaw" cells and thus disinhibit the PTN's.

D. Phenomenology of Paradoxical Sleep in Cats: M. Jouvet

In his presentation, Dr. Jouvet reported on his extensive studies of paradoxical sleep in cats, experiments from which a great deal has been learned, not only about the phenomenology of this particular phase of sleep, but also about its mechanisms and the effects of its deprivation. The former aspect of his presentation will be discussed in this section, while the latter will be taken up on pages 38-43.

As mentioned earlier, paradoxical sleep is also often referred to as "fast-wave low-voltage sleep," "desynchronized sleep" or "activated sleep." Jouvet has found that this particular state, which usually appears periodically after an initial stage of slow-wave sleep, is characterized by an EEG pattern very similar to (but not identical with) that during activation in the waking state (Fig. 7). Jouvet mentioned at the outset of his presentation that in his opinion "paradoxical sleep and slow-wave sleep are two kinds of different phenomena," and that "paradoxical sleep is as different from slow-wave sleep as slow-wave sleep is different from waking." According to Jouvet, paradoxical sleep in the cat is quite similar to paradoxical sleep in man. A low-voltage fast-wave pattern dominates the EEG as it does during waking. Unlike the waking state, however, high-voltage spikes occur in the occipital leads. Further, paradoxical sleep is characterized by theta waves (4-6 per second) in the hippocampus, monophasic spikes intermingled with theta waves in the pontine reticular formation, and high voltage spikes in the lateral geniculate body. The electromyogram of the neck muscles is quite flat, in contradistinction to slow sleep and wakefulness. Rapid eye movements occur up to 120 times per minute; the heart rate is slowed, though it is quite irregular, and often episodes of tachycardia occur; narrow pupils and relaxed nictitating membranes complete the picture. For experiments in which the brain above the pre- or postpontine level has been removed,

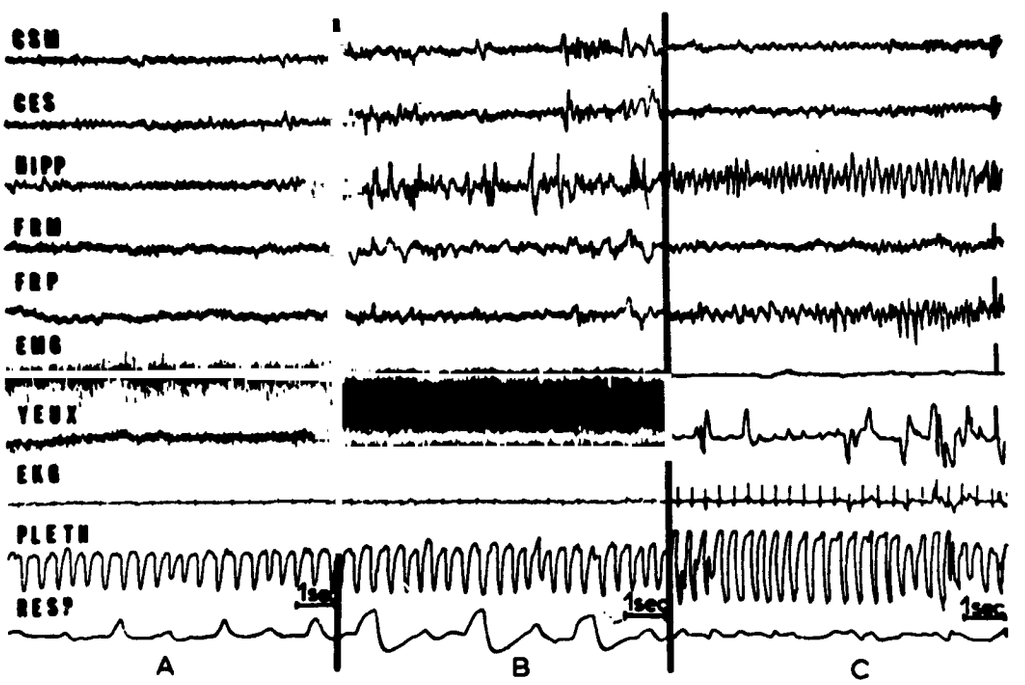

Figure 7. Physiological and electrographic signs of waking and of the two phases of sleep in the intact cat. A (left side): waking animal; note rapid cortical and subcortical electric activity, activity in neck electromyogram. B: slow-wave, high-voltage sleep with cortical spindles and delta waves, spikes in hippocampus and slow waves in reticular core; slight reduction in neck muscle myogram. C: fast-wave, low-voltage sleep; cortical EEG's similar to those during waking; theta rhythm in hippocampus and in pontine reticular nuclei; atonia in neck muscles; rapid eye movements, bradycardia and irregular breathing; increase in plethysmographic index. CSM: sensory motor cortex; CES: ectosylvian gyrus; FRM: midbrain reticular formation; FRP: pontine reticular formation; EMG: neck muscle myogram; HIPP: hippocampus. YEUX: electrooculogram; EKG: electrocardiogram; PLETH: plethysmogram forepaw; RESP: respiration; Calibration: 1 sec, 50 μV. [From: Jouvet, M. (1963): Electroenceph. Clin. Neurophysiol. Suppl. 24:133-157.]

the peripheral indicators, such as neck muscles and heart-rate, are of utmost importance in determining the presence or absence of paradoxical sleep. In "pontine" cats (i.e., those whose brain above the prepontine level has been removed), electrical recordings from the pontine reticular formation add more indicators for paradoxical sleep.

In normal cats, paradoxical sleep episodes also occur in periods that appear quite suddenly after episodes of slow-wave sleep, and last about six minutes. They cover about 15% of a full day, i.e., about 35% of the 45% of total sleeping time of these animals.

Another aspect of Jouvet's work, his studies of the pattern of recovery from paradoxical sleep deprivation, will be discussed on pages 38 to 43 particularly as these studies cast light on the "function" of paradoxical sleep.

E. Electrophysiological Phenomena and Sleep: Ultraslow Potential Changes: V. Rowland

Dr. Rowland, in reporting and interpreting experimental findings from his laboratory, covered several aspects of sleep and wakefulness, sleep-inducing (and-inhibiting) stimuli, as well as conditioning experiments related in one way or another to sleep. The latter two aspects of Rowland's findings will be described and discussed later in their proper framework (see pages 59 - 61). This section will deal with more phenomenological findings having to do with d-c recording of sustained potential variations, often referred to as "ultraslow electrical potential changes." The pioneering work in this field has been done by the German physiologist, Caspers[6], who studied rats chronically prepared with non-polarizable electrodes. This investigator observed that cortical electrodes, if measured against an "indifferent" bone electrode, exhibit a negative potential difference, which decreases somewhat (i.e., the cortical electrode shifts toward "positivity") with slow sleep, and decreases to an even greater extent with paradoxical sleep.

In Rowland's opinion the situation is much more complex than that described by Caspers. First, "no electrode has yet been proved to be indifferent." In Rowland's laboratory, after a large number of epicortical, intracortical and subcortical electrodes are implanted, the "reference electrode is selected, on the basis of that position which, when all other points are recorded against it, gives the greatest

variety of baseline changes, assuming that only the quietest electrode can do this." One is particularly assured of reasonable quiescence at the reference, if two sites recorded against it show opposite polarity and nearly equal amplitude shifting. "Reference" electrodes were often also mounted on the occipital bone, while the investigators were aware that "the skull is not immune" to d-c shifts in the underlying brain tissue.

Russell Durkovic, in Rowland's laboratory, found that with most electrode settings and recording against the occipital bone, a negative shift occurs with the onset of REM periods, though there are local differences. Rowland described one case in which an electrode just beneath the surface of the post-cruciate gyrus cortex was non-responsive; another electrode, however, in the same location about one millimeter below exhibited, with onset of REM sleep, a negative shift of several hundred microvolts which endured throughout the whole REM sleep episode and then "went positive" when the REM period was terminated. In the same animal two electrodes mounted vertically above one another in the visual cortex exhibited negativity against occipital bone with the onset of the REM period.

In another cat, electrodes mounted in the hippocampus also shifted toward negativity with the onset of REM periods, and with waking. Rowland also pointed out that Durkovic's findings of negative shifts during REM's confirm those of other authors - such as Kawamura and Sawyer[7], and Würtz.[8]

In trying to explain the difference between Durkovic's findings and those of Caspers, Rowland pointed out that the experiments were done in two different species (rat vs. cat) and that the condition of the reference electrode in Caspers' work was not known. He also mentioned that he would not claim that his own findings fully prove negativity "coming in" with REM's, as the remote possibility exists that his readings may indicate positivity at the reference site: "Several triangulation combinations would be needed to establish, by the rule of parsimony, true negativity at the cortical electrodes."

F. Energy Metabolism and Activity of Biogenic Amines in the Brain During Sleep and Wakefulness: S. Kety

Dr. Kety discussed the question of metabolism during sleep, in particular the O_2 metabolism of the brain, and the

metabolic and functional role of a number of biogenic amines in the brain. His first topic, blood flow and O_2 uptake by the brain in sleep and waking, was based primarily on his own studies of about 15 years ago. He mentioned briefly that at that time many experimental neurologists still had the idea that sleep was the result of ischemia or anoxemia or that sleep was a kind of narcotized state induced by a hypothetical "Schlafsubstanz." Kety also mentioned Sherrington's[9] idea, current at that time, that there was generalized inactivity in the brain during sleep.

Together with Mangold, Conner, Sokoloff, Kleinermann, and Therman, Kety (1955) used the nitrous oxide technique to study the cerebral blood flow and oxygen consumption of the brain in sleep, as compared with other states. The EEG and clinical indicators were used to distinguish sleep from several stages of wakefulness, including resting, fatigued states, activated wakefulness, and "hyperalerting" in anxiety states. The findings as to blood flow and oxygen consumption are presented in the following table:

Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate for Oxygen ($CMRO_2$) During Various States of Vigilance

	Fatigued Awake	Sleep	Normal Rested
EEG		Slow Waves Spindles	
CBF (Ml/100 g brain/MM)	59	65	55
$CMRO_2$ (Ml/100 g brain/MM)	3.5	3.4	3.3
Art. pO_2 (Hg)	19.4	19.4	19.4
Art. pCO_2 (Hg)	46	46	41

These very striking findings demonstrated for the first time that during a physiological state of "depression" there is no essential drop in O_2 consumption, while in other, pathological states of depression, i.e., coma, there is a marked drop of O_2 uptake (about 1.9 to 2.3 ml). Other of Kety's findings dealt with the blood/gas tension of pO_2 and pCO_2. These results are also presented in the table above. Certainly all these findings would rule out any speculation that sleep has to do with cerebral anoxemia and ischemia. Furthermore, Evarts' (1960) findings, together with many others' would a priori rule out Sherrington's notion of cerebral rest

during sleep, and confirm W. R. Hess' much older idea (1924-25) that sleep is an active phenomenon induced by excitation of sleep-inducing and -controlling structures.[10]

An interesting chance observation in Kety's work concerned the CO_2 tension in the blood. While fatigued subjects who (later) fell asleep showed an increase of the blood CO_2 to 46 mm Hg, fatigued subjects who later could not fall asleep showed a blood CO_2 tension comparable to that of restful, non-fatigued wakefulness (41 mm Hg).

Kety then also mentioned briefly the work of Lübbers[11] and his collaborators, who have measured cerebral oxygen consumption in dogs with a different method. They found with a shift from wakefulness to sleep, only a slight reduction, by 20% or less, of O_2 consumption. Sleep was induced in these studies by small doses of anesthetics.

Birzis and Tachibana,[12] according to Kety, measured local cerebral flow with the (still somewhat controversial) impedance pulse methods in cats. They found that alerting (by noise, light, or smell of fish) led to a highly localized and significant increase of the impedance pulse in the posterior hypothalamus, signaling an increase in local blood flow. In light sleep there was an increase in impedance pulse in the cerebral cortex and reticular formation, whereas the indicator decreased in the hypothalamus. In deep (slow-wave) sleep there was an increase in all areas probed, and in paradoxical sleep the impedance pulse again showed a pattern similar to that observed during the waking state. Kanzow[13], using a thermal conductivity method, reported a marked increase in cortical blood flow during paradoxical sleep in cats.*

Kety then discussed the metabolism and the possible role in sleep of a number of biogenic amines. He first mentioned the still somewhat controversial story of gamma hydroxybutyrate, a congener of GABA (gamma aminobutyric acid). Wolf,[14] as well as Bessman and Fishbein[15] had found this substance in the brain, whereas Giarman and Roth[16] were

* Note added in proof (May 2, 1966): In preliminary experiments using an autoradiographic technique, Reivich, Evarts and Kety have found a remarkable increase in blood flow of the order of 100% in various structures throughout the brain, including subcortical nuclei, during paradoxical sleep. (Kety)

unable to detect it there. If this compound were indeed present in the brain, it would be of great interest because of its pharmacology: gamma hydroxybutyrate, a few minutes after its intravenous administration, produces sleep that behaviorally does not differ from normal sleep.[17] Experimental subjects awaken readily and are immediately clear-headed. The hypnogenic effect of this compound is thus quite different from that of the barbiturates. Gamma hydroxybutyrate also does not produce the state of "semi-narcosis" with its typical grogginess and relative disinhibition. (Laborit[17] reports that it can, if used with premedication, serve as an anesthetic.)

Kety then spent the remainder of his presentation discussing "classical" biogenic amines, particularly, norepinephrine (noradrenaline), epinephrine (adrenaline), and serotonin (5-HT). He started out by mentioning the effect of reserpine, which has been known for some time to produce sedation (not true sleep), and to induce a marked fall of brain catecholamines and other amines such as serotonin and tryptamine. Further, administration, to such sedated animals, of DOPA* (a precursor of dopamine, and thus a precursor of norepinephrine) together with a monoamine oxidase (MAO) inhibitor induces arousal together with an increase in brain catecholamines. This evidence of correlation between arousal from reserpine-induced sedation and the increase in catecholamine content in the brain led to the notion that catecholamines are involved in arousal; but there is still some controversy whether other amines are involved, too. Reason for reservation in accepting this catecholamine notion may also be found in the observation that reserpine as well as monamine oxidase inhibitors have very different effects in different species.

Kety proceeded then to discuss some work on the metabolism of norepinephrine (NE) in the brain. He pointed first to the difficulty of studying norepinephrine -- one cannot get the substance into the brain across the blood-brain barrier (BBB). Thus, injection of radioactive NE, which might seem useful to study the fate of this compound, leads to only minute deposition of the tagged substance in the CNS. Dopamine, a NE precursor, does not penetrate the BBB any better. Even injection of radioactively tagged grandparent (DOPA), and great-grandparent (tyrosine), which do cross the BBB, does not allow the accumulation of radioactive NE in amounts necessary to study its metabolism. Glowinski and Axelrod[18] found,

* 3,4-dihydroxyphenylalanine

however, that one hour after intraventricular injection of radioactive NE, the tagged compound is taken up by the brain in a topographical as well as intracellular distribution similar to that of naturally occurring endogenous NE.

In working with the little-understood CNS catecholamines, it is helpful to apply knowledge about the better-known peripheral adrenergic nerves. It is well established that in peripheral adrenergic nerve endings the NE is stored in small vesicles and is being acted upon by MAO to be converted to deaminated products. On the other hand, nervous impulses reaching the nerve terminals also release NE from the vesicles; it then reaches the synaptic space, interacts with the receptor at the postsynaptic membrane and is then metabolized by catechol-O-methyl transferase to form the methyl derivative, normetanephrine. With reserpine, deaminated products increase in the brain, suggesting that with this drug the spontaneous leak of inactive NE is increased, thus reducing the active concentration at cerebral synapses. Amphetamine treatment, however, leads to the appearance of methylated products in the brain, while sympathetic stimulation leads to appearance of the methylated products in the periphery. Both observations strongly indicate that nerve stimulation as well as amphetamine elicit the release of active NE.

G. Short- and Long-Period Rhythms in the Sleep-Wakefulness Pattern: F. Halberg

Dr. Halberg discussed some results of the approach by spectral analysis* to neural and other rhythms with respect to the sleep-waking pattern. He noted a broader-than-classical spectrum of rhythms in sleep-wakefulness per se and in other body functions, including those depicted by electrocorticograms. These rhythms are detected and quantified by electronic computer techniques developed especially for this purpose. He

---

* As a crude analogy, the spectrum of physiologic rhythms can be compared with the spectrum of electromagnetic radiation which describes the spectral intensity distribution of the constituent oscillations with different frequencies--including among other components the oscillations resulting in visible light. By the same token, physiologic spectra describe the extent to which the "intensities" or the amplitudes of biologic oscillations with different frequencies contribute to the total variability encountered in serial biologic measurements. Like electromagnetic ones, physiologic spectra cover a broad frequency domain. (Halberg)

also suggested that physiologic endpoints heretofore unavailable result from the application of these methods. The view of a spectral structure of organisms, revealed by their rhythms, can be documented from work with such spectral endpoints; against this background one can then explore a temporal physiology and pathology of the central nervous system. Rhythms with frequencies well known from the behavior of sleep and wakefulness, namely a) circadian rhythms (in the region from one cycle in 28 h to one cycle in 20 h) and, b) ultradian rhythms (in the region from one cycle in 20 h to one cycle in about 1 h), can be examined in data displays as a function of time (see Fig. 8) and preferably, also, by so-called spectral methods and derived measures such as circadian quotients (CQ).

He noted that both the behavior-day charts and the CQ's of infants raised on a self-demand schedule reveal that immediately after birth, frequencies in the ultradian region of the spectrum are more prominent than circadian frequencies. With advancing age, the circadian rhythm predominates increasingly over the ultradian one: infant development involves a circadian-to-ultradian variance transposition that can be objectively gauged by the circadian quotient or CQ. The so-called free-running of the circadian component in the spectrum of the developing infant -- suggested by the data in the top portions of the charts in Fig. 8 -- also can be gauged by spectral analysis (spectra not shown).

Halberg demonstrated how variance spectral estimates detect and quantify an effect of reserpine upon the circadian component in human rectal temperature, an effect occurring in the absence of gross changes such as fever or hypothermia -- as reported elsewhere (Halberg, 1963.)

He discussed the rather drastic circadian periodic changes in the susceptibility to audiogenic convulsions and to death from convulsion of certain inbred strains of mice. These animals are bred for periodicity analysis by the temporal biologist just as fruit flies are maintained by geneticists. With such models available, other agents, a number of them traumatizing the central nervous system, also can be shown to exhibit effects that depend upon the phase of the circadian system at the time of exposure. Thus, he suggested, the stage of circadian periodic organization predictably taps the scale between death and survival from a fixed dose of agents such as ethanol, acetylcholine, or the psychotropic drug librium, among others studied by Scheving[19], Davis[20], and Wooley and Timiras[21].

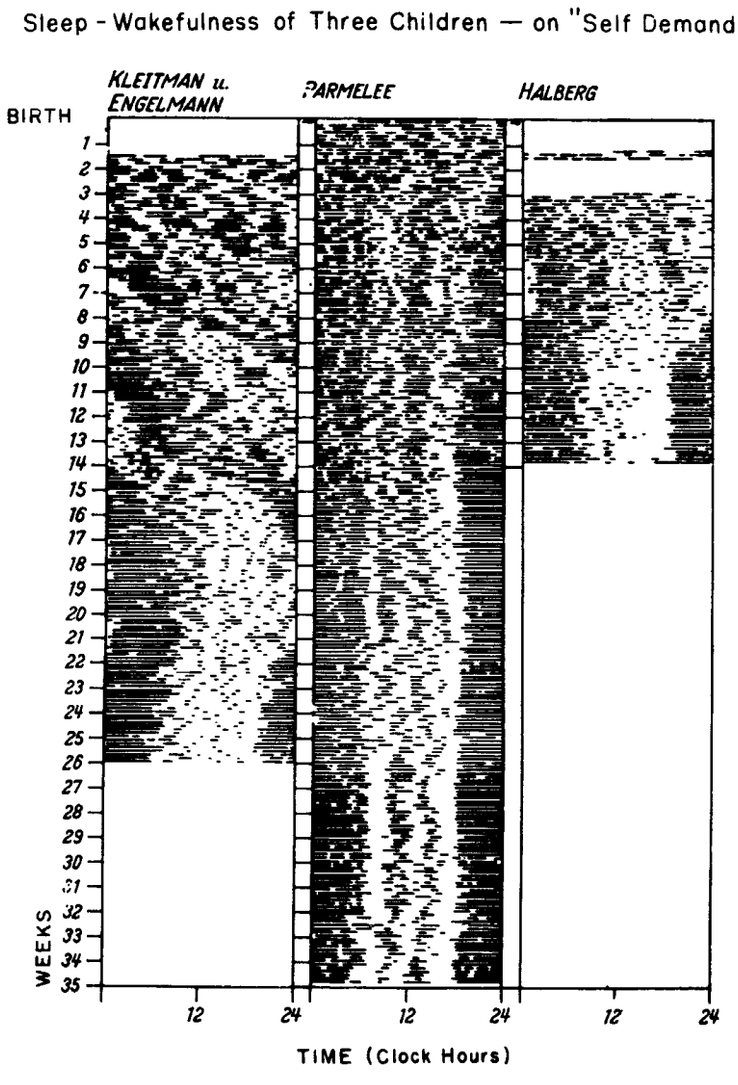

Figure 8. Three behavior-day charts, aligned by Hellbrugge. [Halberg]

In view of the experimental demonstration that the circadian system critically determines various responses of the central nervous system while it also provides a rather sensitive gauge of drugs affecting the central nervous system (e.g., reserpine, see above), Halberg suggested that one can now use as endpoints the sample amplitude and the sample phase of the electro-cortical rhythms as well as of metabolic ones related to neural and neuroendocrine function. These endpoints do indeed describe statistically significant changes, revealed -- for the case of the electrocorticogram of the mouse -- by mere spotchecks, such as those described by R. Harner[22]. A neuroendocrine "division-of-labor" in time is revealed by reliable phase differences based on extensive transverse mapping of certain neuroendocrine functions.

Halberg noted that on the basis of so-called transverse profiles, namely of series obtained on comparable individuals over spans not much longer than the period under study, the mapping of pertinent circadian rhythms in man also has begun, in terms of frequency spectra -- and also as polar phase diagrams. Such data can be analyzed by electronic computer programs to study variance transposition or circadian desynchronization as aspects of a temporal pathology.

According to Halberg, longitudinal profiles, consisting of series covering spans that are much longer than a given physiologic period under study, are amenable to rigorous analysis by the same electronic computor techniques, e.g., by polar amplitude phase as well as by temporal amplitude and phase diagrams. He reported that under the conditions of synchronization with an institutional routine, there is a rather remarkable stability of phase in the face of a rather plastic amplitude in certain of the component rhythms of the circadian system. These findings of relative stability in circadian phase have been extended to the circadian time estimation and heart-rate rhythms of healthy subjects living for several months in the isolation of a cave, without known time cues.

Halberg pointed out that in view of the relative stability of circadian phase in health, phase alterations in disease gain in interest. He suggested as a pertinent model of such chrono-pathology, the consistent change in phase of the rectal temperature rhythm after blinding -- the original model for a circadian phase-drift of about a decade-and-a-half ago having been studied recently elsewhere with confirmatory results.

III. MECHANISMS OF SLEEP INDUCTION, MAINTENANCE AND TERMINATION

A. Anatomical Substrates of Central Nervous Control Mechanisms Subserving the Sleep-Wakefulness Cycle: G. F. Rossi

Dr. Rossi gave an account of his experimental studies which, much like the studies of Jouvet (see pages 38-43), have been conducted primarily by the method of surgical dissection. Rossi's work has led to a detailed spatial concept of the functional subsets within the overall sleep-wakefulness mechanism, a concept which is fully compatible with the notion that sleep is not merely a passive state of the central nervous system. Rossi has identified "passive" as well as "active" sleep mechanisms and has, moreover, provided suggestions as to the possible modes of interaction between the two categories. The resultant concept is illustrated in diagrammatic form in Fig. 9 . The right half of the diagram shows the approximate extent and location of those brain stem structures that appear to be essential for arousal and maintenance of vigilance (block A). The region in question occupies a large territory in the brain stem tegmentum. Its lower border appears to lie at the upper pontine level, rostrally it extends throughout the length of the diencephalon.

The location of structures critically involved in mechanisms of induction and maintenance of sleep states is indicated in the left half of Fig. 9 (horizontal lines). Structures within this category are strung out over a larger extent of the brain stem involving, among others, the pontomedullary tegmentum in which no structures essential to the maintenance of the wakeful state have been identified. A distinction must here be made between components subserving synchronized or slow-wave sleep (indicated by horizontal lines) and the somewhat separate but undoubtedly closely associated pontine mechanism related to the paradoxical or desynchronized phase of sleep (cross-hatched block D).

Physiological observations following surgical involvement of various CNS levels can be summarized as follows: Following brain stem transection at the midbrain level, the forebrain ("cerveau isolé") does not exhibit the normal periods of desynchronized electrocortical activity characteristic of the waking state. Rather, its condition is reflected in a protracted state of electrocortical synchronization and of behavioral unresponsiveness: coma. The most caudal brain stem transection followed by similar electrocortical and

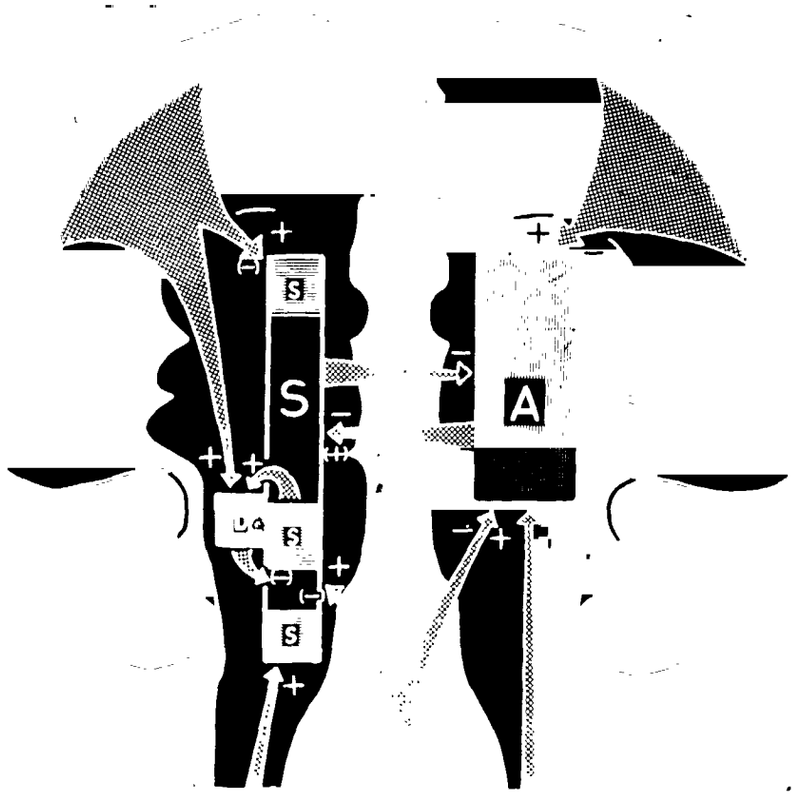

Figure 9. Schematic representation of "active" and "passive" sleep mechanisms and their possible interaction, according to Rossi.

behavioral effects is at the level of the upper pons.[23] With the passage of time, however, periods of EEG and behavioral arousal reappear. Arousal is permanently abolished only if the diencephalon is destroyed. These findings suggest that the arousing structures are distributed all along the rostral part of the brain stem and the diencephalon.

Integrity of the thalamus is an essential prerequisite for the occurrence of the most characteristic EEG figure of synchronized slow-wave sleep, the "spindle." There is evidence that EEG synchronization is dependent upon interactions between thalamus and cerebral cortex, for complete bilateral decortication likewise abolishes the phenomenon of EEG synchronization (Jouvet, 1962) although it does not interfere with the phenomenon of desynchronized (paradoxical or REM) sleep. It is an interesting, and, so far, open question whether this finding proves that decorticate animals live in a state of persistent wakefulness interrupted only by episodes of paradoxical sleep.

Below the thalamocortical level, other mechanisms of fundamental importance for the phenomenon of synchronized sleep have been identified. Batini, Moruzzi, Palestini, Rossi and Zanchetti,[23] found that brain stem section at the mid-pontine level in cats produces a state of long-lasting EEG desynchronization and behavioral wakefulness. Subsequent studies by Rossi and co-workers have localized the pontine sleep-inducing mechanism in the reticular formation of the pontine tegmentum. Synchronizing mechanisms have also been identified in the medulla oblongata[24]; the localization of the structures involved at this level appears to correspond to the region of the solitary tract and the adjoining reticular formation. It is interesting that both the pontine and medullary regions in question coincide with the location of neurons known to emit long axons ascending beyond the midbrain level (Brodal and Rossi, 1955). Rossi has therefore suggested the possibility that the rhombencephalic sleep-inducing structures are characterized by having predominantly oligosynaptic connections with the forebrain, whereas the EEG-desynchronizing mechanisms are, by contrast, made up of more polysynaptically organized neuronal chains. This suggestion is compatible with the observation that the synchronizing systems are most effectively activated by low-frequency stimulation, whereas arousal is more easily elicited by stimulation at high frequencies.

Jouvet (1962) was the first to report the disappearance of both the EEG and behavioral manifestations of desynchronized sleep following extensive destructions of the pontine tegmentum. According to Rossi's observations, the structures most immediately associated with desynchronized sleep are located at the mid-pontine level, where they overlap to some extent with the pontine substratum of synchronized sleep.

The findings described above indicate that all levels of the brain stem are involved in the neural process of sleep and wakefulness. Sleep-inducing structures, however, are more widely distributed than are the arousal mechanisms; the latter appear to be represented only rostral to the mid-pontine level (Fig. 9). There is good reason to believe that arousing and sleep-inducing structures are closely interconnected anatomically as well as functionally. Their interaction appears to be in part one of reciprocal inhibition, but the experiments of Dell and his co-workers[25] have suggested the additional existence of "negative feedback" mechanisms which may result in facilitation of sleep-inducing mechanisms as a result of extended activity of the arousal system. Similar interactions may exist between the synchronizing and desynchronizing subsets of the sleep mechanism: desynchronized sleep episodes never appear independently, i.e., without a foregoing period of synchronized sleep, either under physiological conditions or in stimulation experiments.

Both the arousing and sleep-inducing mechanisms can be activated by neural impulses originating in other central structures such as the cerebral cortex, or in the sense organs. Such influences are mainly phasic in nature, but at least one sensory system, the trigeminal input, appears to have a more tonic facilitating effect on the arousal mechanism (Roger, Rossi and Zinandoli, 1956). Electrical stimulation of the cortex may result in either arousal or sleep induction. Depending on frequency of stimulus and on pre-existing functional states, either effect can be induced by stimulation of one and the same cortical region. Rossi and co-workers have also observed the triggering of desynchronized sleep episodes from the cerebral cortex, but only when the stimulation was given against a background of well-developed synchronized sleep.

The importance of stimulus parameters is even more evident in the results of peripheral sensory stimulation. In general, sensory inputs elicited by low-frequency stimulation favor sleep induction; whether this takes place by activation

of central sleep-inducing mechanisms or by inhibition of the arousal system is undecided. Some sensory inputs, such as those resulting from stimulation of proprioceptor or of type III cutaneous afferents, appear to cause arousal irrespective of stimulus parameters; conversely, stimulation of baroreceptor afferents tends to favor sleep induction.[26]

At least three neural phenomena may account for the shift from waking to synchronized sleep: 1) neuronal fatigue occurring within the arousing structures; 2) decreased afflux of excitatory impulses to the arousal mechanisms, both from the peripheral sense organs and the cerebral cortex, or 3) increased activity of the sleep-inducing structures, possibly favored by monotonous stimulation. Not yet classified are the mechanisms responsible for the episodic appearance of desynchronized (paradoxical) sleep periods. Rossi interprets these episodes as abrupt interruptions of the development of at least some of the neural events underlying synchronized sleep; something new appears in the brain, though there is a further deepening of the sleep state, at least in the cat. In Moruzzi's[27] opinion, desynchronized sleep appears to be a period during which consumption takes place of something accumulated during synchronized sleep. It is quite likely that this "something" will eventually be identified as a humoral rather than a neural phenomenon.

B. Controlling Structures and the Effects of Paradoxical Sleep Deprivation: M. Jouvet

Dr. Jouvet has attempted to isolate the two fundamentally different forms of sleep (synchronized or slow-wave, and desynchronized or paradoxical), in an attempt to elucidate the functional significance of desynchronized sleep. He described a surgical preparation in which synchronized sleep was abolished by removal of all the brain (mesencephalon and forebrain) rostral to the pons. Such preparations show periods of "waking" (in reality a state of decerebrate rigidity), alternating with desynchronized sleep episodes, the latter being identifiable by disappearance of muscle tonus in the neck coinciding with rapid eye movements transmitted via the abducens nerve (the only oculomotor nerve left intact). Truncation of the brain behind the pons abolishes the desynchronized sleep episodes, an observation suggesting that the neural mechanism underlying the phenomenon of desynchronized sleep is located at the level of the pons. More detailed studies have shown that in the otherwise intact brain, such sleep episodes are eliminated by bilateral lesions in the

dorsolateral pontine tegmentum. It therefore seems likely that the phenomenon of paradoxical or desynchronized sleep is dependent upon the integrity of a particular neural organization in the pontine reticular formation.

With suitable precautions, animals decerebrated rostral to the pons ("pontine cats") can be kept alive for months, provided an island of hypothalamus is left connected to the hypophysis. In such preparations, "oneirograms" have been made by the aid of an integrative mechanism activating a polygraph at the onset of neck muscle atonia, and thus allowing the selective recording of paradoxical sleep episodes. Recording was from the pons and from the eyeball and thus included brain stem EEG (monophasic spikes superimposed on theta waves) and lateral eye movements; it was terminated by the return of neck muscle tonus. By this method, the "paradoxical sleep cycle" of pontine cats, recorded continually for many days, was found to consist of episodes of 6 minutes mean duration, making up 10% of the 24-hour day, occurring as frequently during the day as during the night. By comparison, in normal cats the average duration of such episodes is 6 minutes, 20 seconds, making up 15% of the 24-hour day, and the episode frequency is higher during the night than during the day (probably related to distracting events in the daytime).

The question as to what afferent signals, if any, precipitate the paradoxical sleep episode has been studied extensively. Jouvet finds that the occurrence of such episodes is unaffected by removal of the cerebellum, mesencephalon, diencephalon, or hypophysis. The phenomenon also persists following section of the vagus and glossopharyngeal nerves, the C1-C7 dorsal roots, or vestibular nerve. Resection of the stellate ganglia or spinal cord section at Th 1 likewise has no effect on the paradoxical sleep phenomenon.

Rossi inquired about some of the physiological effects of these operations. Jouvet replied that while no effects seem to be specific, bilateral vagus section is followed after a week by respiratory difficulties. This condition may in turn lead to a decrease in total paradoxical sleep time. Further, removal of the hypothalamo-pituitary "island" left in cats otherwise deprived of all brain rostral to the pons, precipitates a rapid decline of the animal's general condition, due to ionic imbalance. Such dying animals likewise show a decrease in total paradoxical sleep time (to 3%), an unspecific effect, in all likelihood, since a single daily injection of 2 units of ACTH and 90 units of pitressin restores the normal percentage of paradoxical sleep.

Body temperature has a remarkable effect upon the paradoxical sleep cycle. If, in a "pontine" cat, the temperature is allowed to fall from the normal 39.5° C to near 30° C, the duration of each paradoxical sleep episode increases from 6 minutes to approximately 20 minutes; at the same time, however, the interval between such episodes is widened from 30 minutes to 80 minutes, resulting in no marked change in total time spent in paradoxical sleep.

Another factor profoundly affecting paradoxical sleep appears to be related to mechanisms regulating the water balance. Pontine animals that were fed a mostly liquid diet were found to show a decrease in the total paradoxical sleep time from 10% per day to 3%. Conversely, intravenous administration of hypertonic saline was found to result in increases to as much as 25% paradoxical sleep time. These effects are most marked in animals in which a hypothalamo-pituitary island is left, but they are noticeable also in purely "pontine" cats. The injection of anti-diuretic hormone appeared to have no effect. Jouvet therefore believes that the phenomenon is due to a direct effect of blood osmolarity upon the osmolarity of the brain.

Koella here suggested the alternative possibility that certain strategically located neurons might respond selectively to changes in blood osmolarity. This is suggested by the well-documented susceptibility to hypotonic solutions shown by the medullary region adjoining the area postrema.(28)

Together with his collaborators, Jouvet has studied the effects of artificial deprivation of paradoxical sleep by having cats spend periods of from one to 22 days on a platform too small for complete relaxation, surrounded by a moat of water. The sleep records of animals kept under such conditions show approximately the normal amounts of slow-wave sleep (42%) during each 24-hour-day period, without intervening episodes of paradoxical sleep. The paradoxical sleep deprivation was found to have profound physiological effects: the cats gradually developed a tachycardia (60%-80% above normal), became photophobic, showed evidence of increasing muscular weakness, and had an increased need for food and water. One cat, deprived for 26 days, died,apparently of exhaustion.

Following the deprivation period, cats recover the lost paradoxical sleep time in almost exactly half the deprivation time. This recovery is achieved as follows: On the first day there is an increase in both length and frequency of paradoxical sleep episodes. Thereafter, each episode resumes the normal duration of approximately 6 minutes, but the frequency of episodes continues to be elevated. The amount of paradoxical sleep can be as high as 60% of the total sleep time during the first 6 hours of recovery, but it has never been seen to exceed this level, even after 22 days of deprivation. Jouvet concludes that if paradoxical sleep is indeed the manifestation of a mechanism subserving the elimination of some accumulated chemical substance, this elimination is an inherently periodical phenomenon.

Dr. Schmitt remarked that Jouvet's periodicity charts suggest a linear relation between the deprivation and the instalments used to repay the debt. Jouvet agreed with this, but remarked that somehow, the debt never seems to be completely repaid. Even as long as a year after the experiment, a cat subjected to severe paradoxical sleep deprivation can be easily identified by some enduring change in facial expression, a certain look of suffering.

Dr. Williams here mentioned his observations in humans subjected to complete sleep deprivation of moderate duration (about 70 hours). Following such deprivation periods, humans tend to make up for the loss of stage IV (synchronized) sleep well before the paradoxical sleep debt is repaid. They recover about 50% of the stage IV deficit during the first night of undisturbed sleep, 50% of the residual during the next night, and so on in an approximately linear exponential schedule. The paradoxical sleep recovery shows a different curve: over a 4-night observation period, paradoxical sleep is most often slightly subnormal during the first night, and well above normal quantity in the 3 following nights. In a man subjected to extreme sleep deprivation, on the other hand, Dement observed a marked increase in REM sleep time already during the first recovery night; this increase was still evident 4 days later.

Jouvet next described a pattern of sleep in cats similar to that described by Dement and Rechtschaffen(1966) as characteristic of narcoleptic episodes in human patients. This phenomenon is characterized by a direct transition from waking to paradoxical sleep, without the normal interposition of a slow-wave sleep period. Jouvet has observed this

phenomenon of "narcoleptic" sleep in several cats recovering from protracted periods (18 days and over) of paradoxical sleep deprivation.

In the pontine cat, it is nearly impossible to suppress paradoxical sleep, even by the method of delivering painful electric shocks at the onset of paradoxical sleep episodes. In normal cats, this experimental procedure continued for 3 hours results in increasing frequencies of up to one paradoxical sleep episode (aborted by the experimental procedure) per minute.

Total suppression of the paradoxical sleep mechanism can be obtained by appropriately localized pontine lesions. Following such lesions, cats still show a normal alternation of waking and slow-wave sleep. After two weeks of this chronic loss of paradoxical sleep, a peculiar form of behavior appears during the slow-wave sleep period, characterized by massive, well-organized movements suggesting fight or escape behavior, but paradoxically accompanied by the pupillo-constriction characteristic of sleep. Peculiarly, the EEG record during such episodes becomes "flat" (low-voltage, desynchronized) once more, suggesting either wakefulness or paradoxical sleep. In this state, the cats do not respond to external stimuli. Although it is difficult to characterize the condition as sleep, nevertheless the phenomenon consists of a curious mixture of sleep and vigilance symptoms; Jouvet is inclined to interpret it as a state of incomplete paradoxical sleep, i.e., a paradoxical sleep which lacks the characteristic muscle atonia.

Dr. Evarts at this point remarked that the body movements occurring in this condition could be interpreted as evidence of failure of the "uncoupling" mechanism which in normal sleep prevents the transmission of certain neuronal discharges in the brain stem to the neuromuscular apparatus. Jouvet agreed with this view, and added that the pontine lesion in his cats may conceivably have destroyed a neural mechanism normally acting as a trigger for the inhibitory reticular zone of the medulla oblongata. In a discussion between Dement and Evarts, the notion was developed that Jouvet's "hallucinating" cats might show the mirror-image of cataplexy, the latter being a state of muscle atonia dissociated from the rest of the sleep mechanism.

Jouvet finally discussed some neuropharmacological findings pertinent to the paradoxical sleep phenomenon. The

periodic nature of paradoxical sleep suggests that each period is triggered and driven by the accumulation of some chemical principle. On the supposition that monoamines could be involved in this mechanism, the effect of reserpine was studied. In the cat, single systemic injection of 0.5 mg/kilo of reserpine (a substance known to depress the CNS levels of noradrenaline, dopamine and serotonin) was found to result in total disappearance of paradoxical sleep episodes for a period of 5 days, only with a considerable reduction of slow-wave sleep. If the reserpine administration is followed by an injection of DOPA (known to be the precursor of dopamine and noradrenaline), paradoxical sleep episodes reappear over a period of 2 hours; this recovery can be maintained by repeated injections of DOPA. In contrast, 5-HTP (5-hydroxytryptaphan) the presumed precursor of serotonin, does not affect the serotonin-induced loss of paradoxical sleep; instead it increases the amount of slow-wave sleep. Given alone, 5-HTP tends to suppress paradoxical sleep, while increasing slow-wave sleep.

C. Cholinergic and Other Humoral Mechanisms: The Problem of Chemical Specificity in the Neural Substratum of the Sleep-Wakefulness Cycle: R. Hernández-Peón

Dr. Hernández-Peón reviewed his extensive studies of chemical specificity by the technique of local implantation of known transmitter substances in the brain stem of the cat. Hernández-Peón's studies were prompted by his finding that the typical sleep state induced by electrical stimulation of the preoptic region can be prevented by previous systemic administration of atropine. In view of the known anticholinergic properties of atropine, a search was undertaken for brain loci in which sleep could be induced by the implantation of minute quantities of acetylcholine. It was found that within three minutes of deposition of an acetylcholine crystal in the preoptic region by means of a micropipette, cats begin to show behavioral and EEG evidence of drowsiness which rapidly progresses to full-fledged slow-wave sleep alternating with periods of paradoxical (REM) sleep. By systematic further exploration with this technique, Hernández-Peón and his collaborators have been able to outline an extensive mesodiencephalic brain stem region, a point of which, by implantation of acetylcholine can be made the "trigger point" of sleep.

The region in question corresponds in remarkable detail to a neural continuum outlined earlier by the study of neural connections. It extends caudally from the preoptic region

throughout the lateral hypothalamic region and beyond it over a paramedian zone of the midbrain tegmentum (the "limbic midbrain area," Nauta, 1958); its caudal border appears to lie at the rostral pontine level. Hernández-Peón interprets this continuum as the hub of the central sleep-inducing mechanism: the hypnogenic brain stem region. It is interesting that minute quantities of atropine deposited at any point along this central hypnogenic continuum elicit a state of alertness. Moreover, following atropine deposition at caudal levels of the region, acetylcholine is no longer effective as a sleep-inducing agent when implanted at more rostral levels, although its effectiveness at points caudal to the atropinized level is unimpaired. Acetylcholine is likewise ineffective at points rostral to a surgical lesion in the hypnogenic region. These findings suggest that the central hypnogenic mechanism involves impulse transmissions predominately in the caudal direction, i.e., from the preoptic region to the midbrain.

Extending their experiments to other brain regions, Hernández-Peón and his collaborators succeeded in inducing sleep also by implanting acetylcholine crystals at several points in the cerebral hemisphere, specifically the piriform cortex, the orbitofrontal cortex, and the rostral part of the cingulate gyrus, structures known to have either direct or oligosynaptic connections with the preoptic region. However, from other hemispheric structures likewise connected directly to the preoptic area (septal region, amygdala), no sleep could be elicited. Further hypnogenic points were found in the midline region of the thalamus, but negative results were obtained from specific thalamic relay nuclei such as the ventrobasal complex.

Finally, hypnogenic points were discovered far caudal to the central hypnogenic brain stem region, namely in the zona intermedia of the grey matter of the spinal cord at segmental levels C7 and Th 1.

The topographical specificity of the hypnogenic brain and spinal cord regions is remarkable. For example, acetylcholine implantation at hypothalamic sites not more than 2 mm. dorsal to the hypnogenic lateral hypothalamic region elicits a state of angry excitation. Further caudally, in the midbrain, it induces states of restless vigilance when implanted in the reticular formation just lateral to the hypnogenic "limbic midbrain area"; in the dorsal and ventral horns of the spinal grey matter it is without apparent effect,

although it induces sleep when implanted in the closely neighboring zona intermedia.

On the basis of all these findings, Hernández-Peón postulates the existence of a hypnogenic neural mechanism invoking all levels of the central nervous system from the spinal cord to the cortex (Fig. 10). This mechanism can be thought to consist of two main components: 1) an ascending component originating in the spinal cord and extending rostrally through the medulla oblongata and pons, and, 2) a descending component conveying upon the preoptic region from the piriform, orbitofrontal and anterior cingulate regions of the cortex. The preoptic region, in turn, can be interpreted as the rostral pole of a central hypnogenic brain stem region that extends caudally to rostral pontine levels, where it presumably is joined by the ascending hypnogenic pathway. The central hypnogenic brain stem region is known to have numerous anatomical connections with the midbrain reticular formation which flanks it laterally, and its hypnogenic characteristics could conceivably be the expression of inhibitory effects transmitted by such connections to the vigilance mechanisms in the midbrain reticular formation.

In an attempt to verify the specificity of acetylcholine as a central hypnogenic agent, a variety of other neurotropic drugs (GABA, nialamide, barbiturates) were tested. None of these pharmaca were found to have central hypnogenic effects. Although this finding appeared to demonstrate a certain uniqueness in the acetylcholine effects, the suggestion that the hypnogenic regions outlined by Hernández-Peón are characterized by cholinergic modes of transmission nevertheless requires further substantiation. In this connection, Hernández-Peón reported that eserine, an anticholinesterase drug, was found to have hypnogenic properties comparable to those of acetylcholine; conversely, implantation of the acetylcholine-blocking agent atropine in the central hypnogenic region invariably causes awakening and alertness. This evidence indeed appears to favor the notion of a predominantly cholinergic organization of the central hypnogenic mechanism.

In more recent experiments, Hernández-Peón has found that adrenaline and noradrenaline have an alerting effect when implanted locally in the preoptic region, ventromedial hypothalamus, or midbrain reticular formation. These same substances produce a state of agitated arousal when deposited locally within the central grey substance; but acetylcholine deposited at that site likewise causes arousal and a state

Figure 10. Schematic representation of sleep system as described by Hernández-Peón.

of undirected anger, contrasting with the well-directed rage behavior which it elicits upon implantation in the septal region. In Hernández-Peón's experiments, no sleep was found to result from adrenaline or noradrenaline implantation anywhere in the CNS.

The difference in the effects obtained by central implantation of acetylcholine on the one hand, adrenaline and noradrenaline on the other, can be summarized as follows: Sleep can be induced only with acetylcholine, and only from a somewhat circumscript neural continuum (the "hypnotropic region") extending from the cerebral hemisphere into the spinal cord; in several other locations (mesencephalic reticular formation, MRF) acetylcholine elicits a state of restlessness or even angry excitation. Noradrenaline causes alertness when applied to some loci within the hypnotropic region as well as in the MRF; adrenaline elicits this effect only when implanted in the zona intermedia of the spinal cord and is without apparent effect throughout the brain stem and cerebral hemisphere. Hernández-Peón has introduced the term "chemical dissection" to describe this differential activation of mutually antagonistic subsets in the overall sleep-wakefulness mechanism. In this context, Nauta asked if even the "hypnotropic region" outlined by Hernández-Peón might not be interpreted as a mosaic of hypnotropic and vigilance neurons that can be dissected only functionally by virtue of different chemical specificity of component parts. Hernández-Peón replied that, although he agreed there may be a wide spatial overlap between sleep and vigilance systems, there are nevertheless locations where each of these appears to be represented singly, such as the central grey midbrain substance and the dorsal hypothalamic region.

D. Central EEG Synchronizing Effect of Serotonin: W. P. Koella

Dr. Koella described his experiments which supplemented Dr. Kety's report on central biogenic amines. While Kety stressed the importance of the catechol-type amines for the waking state, Koella's data suggested the role of serotonin (5-HT, 5-hydroxytryptamine) for sleep, particularly slow-wave sleep.

In cats anesthetized with Dial and Urethane, flaxedilized and sedated with 1/10 surgical dose of Dial and Urethane or merely flaxedilized, intracarotid injection of serotonin (0.2 to 5.0 μg/kg body weight) induced an initial arousal pattern replaced after 30 to 150 seconds by a protracted phase of hypersynchrony which lasted often as long as 30 minutes.

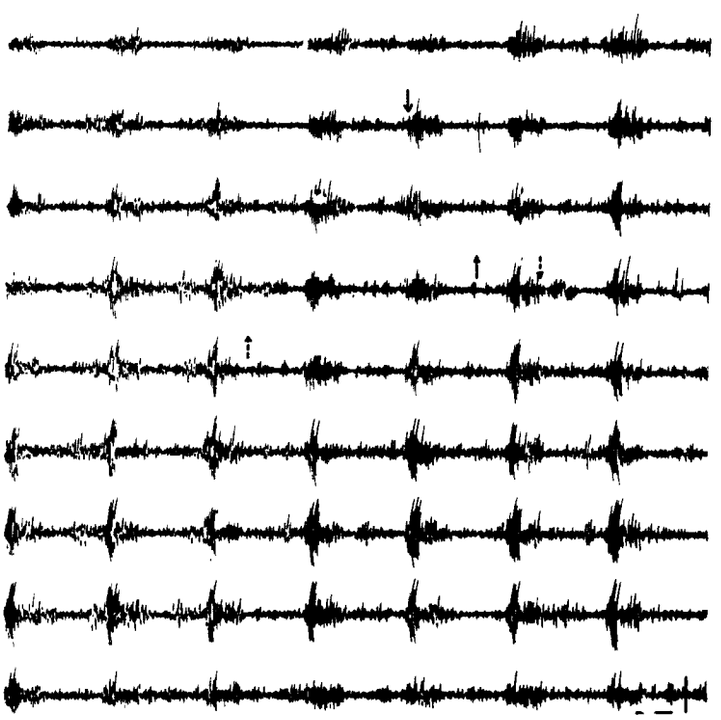

Figure 11. Effect upon recruiting responses of topical application of serotonin to area postrema. Cat immobilized by Flaxedil, artificially respirated and slightly sedated with 1/10 anesthetic dose of Dial. At ↓ cotton pellet soaked in serotonin (1 mcg/cc, total dose about 3 x 10^{-8}g) and applied to area postrema. At ↑ pellet removed. Between dashed arrows area is washed with Tyrode solution. Note marked increase of recruiting responses and appearance of slow waves in interstimulus interval. Calibration: 1 sec, 3 μV. Stimulation in lateral-central thalamus with 1-second trains of pulses at 10 pulses per second Recording from suprasylvian gyrus. [Koella]

Recruiting responses produced by medial thalamic stimulation showed a similar biphasic reaction to serotonin characterized by initial depression followed by often marked and long-lasting enhancement. These EEG changes were accompanied by initial widening then narrowing of the pupils. After transection of the brain stem at the midpontine level, serotonin produced only signs of arousal in the EEG. Intravertebral injections of 5-HT and injections of 5-HT into the fourth ventricle induced only hypersynchronizing effects. (See Fig. 11.) After cauterization of the area postrema or after application of 5-HT blocking agents to the posterior fourth ventricle, the hypersynchronizing effects of intracarotid or intravertebral 5-HT were reduced or altogether eliminated.

Koella concluded that serotonin produces the EEG and ocular signs of synchronized sleep by an action exerted on receptor sites in the area postrema, from which nervous signals travel to the nucleus of the solitary tract and then to more rostrally situated hypnogenic areas.

IV. THE PSYCHOLOGICAL PHENOMENOLOGY OF NORMAL SLEEP

A. Subjective Experience During Sleep: Dreaming: W. C. Dement

The nature of dreaming, a frequent topic of speculation, has in recent years, been increasingly the subject of experimental studies. Dr. Dement reviewed the relation of dreaming to rapid eye movement (REM, paradoxical) sleep, and discussed what is known of the sources of the structure and content of the dream experience.

There is now a considerable body of evidence that demonstrates that the dreaming experience in human subjects occurs primarily during episodes of rapid eye movement sleep. The basic fact underlyin the dreaming-rapid eye movement identity is that sleepers ho are awakened during REM sleep are able to recall dream experiences in a very high percentage of instances compared with controls. (Dement 1964, 1965) In early studies very little dream recall was observed following sleep periods without rapid eye movements. However, as a result of work done by Rechtschaffen and others, it now seems clear that certain types of dreams occur during ordinary sleep.[29,30,31,32] In general, it is believed that the character of dreaming during slow-wave sleep is different from that occurring in REM sleep. Dreaming in the former is abstract and conceptual whereas dreaming during REM sleep has the well-known qualities of concreteness associated with vivid perceptual experience. It is now known that, in the human, the first non-REM period of sleep is the time when sleep-talking, sleepwalking, pavor nocturnis, and even enuresis is likely to occur. When a child suddenly sits bolt upright in bed with a terminal stage IV EEG (slow-wave) hardly dissipating itself, his eyes dilated in terror, it is difficult to deny that some mental event is going on. No one has yet identified a clear physiological indicator of mentation during slow-wave sleep and yet most investigators believe that such an indicator would be needed for systematic investigation of the phenomenon. Some disagreements over the presence of dreaming in sleep other than during the paradoxical phase arise because of special definitions of dreaming. If dreaming is defined to exclude subjective experience and mentation lacking vivid complex sensory imagery, then, of course, it is possible to say that nearly all dreaming is associated with rapid eye movements. It is obviously important to distinguish disagreements over semantic conventions and those over observable phenomena.

Dement cited further evidence for the relation between dreaming and REM sleep based on their respective durations. For fairly short intervals, and in subjects with good dream recall, this relationship is significant and has been confirmed many times. (Dement and Kleitman (1957); Dement and Wolpert (1958)) This phenomenon implies that the dream is an ongoing phenomenon, lengthening itself as time passes in rapid eye movement sleep. Although some people have speculated that dreams may be complex experiences crammed into very short intervals of actual sleeping time, experimental studies show that when a dream is correlated with known events, the rate at which the subjective experience occurs is slower than during a waking period. It is true that on occasion a long time seems to pass in a dream which we know can only occupy a few minutes, but this seems to be based on telescoping and other devices.

Evidence was also presented relating eye movements to the specific content of dreams. One example reported by Dement illustrates this phenomenon. During a sleep study a subject's eyes began to move regularly from right to left; this was, of course, recorded in the tracings made by shifts in eye muscle potentials caused by the eye movements. When the subject was awakened during this phenomenon, he reported that he was in the middle of a dream in which he was watching two mysterious idol-like creatures converse. First one would speak and then the other, and the dreamer felt compelled to pay close attention.

Many eye movements are associated in this way with very active subjective experience. (Dement and Kleitman (1957); Dement and Wolpert (1958); Roffwarg, Dement, et al. (1962); Berger and Oswald (1962)). Such observed phenomena have led to the development of a scanning hypothesis that is still highly controversial. According to the scanning hypothesis, the oculomotor apparatus behaves during dreams as if it were receiving information (sensory input or neuronal barrage) effectively identical with that which elicits the same responses in the waking state. In support of the hypothesis are many episodes like the one cited above. Since the hypothesis has many interesting implications and raises serious questions about the origins of the signals triggering such eye movements, it is worthwhile to discuss the controversy in some detail. One difficulty with the hypothesis is the fact that the intervals between recognizable indicators of "events" (from the eye movements) are slightly longer than we would expect them to be in waking life. This problem disappears if

we can assume that the subjective experience during dreams is a little slower than waking experience. Jeannerod and Mouret[33] in Jouvet's laboratory have studied the rates of human eye movements, and have shown that eye movements during sleep are slower than those observed during the waking state. It is possible that the rate of movement differs when the eyelids are open from when they are shut.

In the waking state the eyes show a characteristic type of movement with alternating fast and slow components when the subject is following a moving object visually. Identification of pursuit movements of this type during paradoxical sleep should support the scanning hypothesis. Roffwarg and Dement (unpublished) attempted to predict the presence of the slow component from dream content; their studies, although partly successful were not conclusive. Experimental studies of pursuit eye movements in hypnotic hallucinations have given conflicting results: Dement and Goldberg (unpublished) did not find them, but Deckert[34] and Brady and Levitt[35] report success. If pursuit movements are present in hypnotic hallucinations, then it is likely for them to occur during dreaming. This issue remains unresolved at the present time.

There are a number of arguments against the scanning hypothesis. Rapid eye movements of a kind virtually indistinguishable from those occurring in adults are seen in newborn infants, who presumably do not dream. (Roffwarg, Muzio, and Dement (1966)) Studies so far reported on congenitally blind subjects present conflicting results. Berger, Olley and Oswald (1962) in one study, and Offenkranz and Wolpert[36] in another, found that, although paradoxical sleep was present by EEG criteria, there were no rapid eye movements. The latter authors awakened their subjects and found no visual dreams. On the other hand, Amadeo and Gomez[37] found rapid eye movements in the sleep records of seven out of eight congenitally blind subjects, most of whom could not voluntarily move their eyes in the waking state. Jouvet (1962) has found rapid eye movements occuring during sleep in functionally decorticated and decerebrate human beings, who presumably do not dream.

Jeannerod and Mouret[33] and their colleagues, in studies of the types of eye movements occurring during sleep, have shown that there is a constant ratio of approximately 50:50 between bursts of movements -- five or more in a sequence -- and single movements. This finding does not support a scanning hypothesis and this observation has been

made both for the cat and the human.[38] It is important, however, to note that eye movements in the cat are quite different from those in the human, and it is quite likely we should not make inferences across species. Berlucchi and his colleagues[39] presented a movie at the Lyon symposium of 1963 showing rapid and nystagmoid movements in the cat that most participants felt could not be based on scanning. Some of these same participants however, now feel that the hypothesis might apply more plausibly to primates and humans than to cats. Human eye movements in sleep are particularly difficult to differentiate from scanning movements. Rechtschaffen (unpublished), who has made direct observations on sleeping human subjects whose eyes were taped open, has stated that the subjects bore an uncanny resemblance to awake subjects.

If rapid eye movements in the waking state and in paradoxical sleep can be shown to have different physiological determinants, then this evidence strongly contradicts the scanning hypothesis. A number of investigators have demonstrated that in the human subject, rapid eye movements are often preceded by what have been called "saw-tooth waves." These may represent some pattern of events in the nervous system, necessary for the eye movements, and yet quite different from the determinants of eye movement during waking periods. In the cat, rapid eye movements are clearly related in time to spike-like electrical activity believed to originate in the pons. Jouvet has concluded that rapid eye movements in sleep may have very little in common with superficially similar movements in the waking state.

With selective deprivation of rapid eye movement sleep in cats, there is a marked increase in the frequency of eye movements. Similar deprivation in humans should increase the amount of dreaming or change the character of the dream. There is little clinical evidence of this type, and if eye movements are blocked by barbiturates in doses that do not stop paradoxical sleep itself, dream recall from subjects does not seem to differ from normal dreaming.

It is not possible at the present time to decide the fate of the scanning hypothesis. It may be that dreaming occupies only part of the time of paradoxical sleep, and that, therefore, only some of the eye movements seen are related to a hallucinatory dream phenomenon. Perhaps the nervous system is operating quite differently during waking as compared to sleeping. Thus, although the eye movements may have some relation to subjective experience, the patterns of organization of the motor phenomena may differ in rate and other character-

istics. It is even possible that the subjective features of the dream are determined by the eye movements rather than the converse.

Other effector mechanisms than eye movements may, of course, be active during dreaming. Muscular twitches occur frequently in the behavior pattern of the cat during paradoxical sleep. This led Dement to suggest at one time that during dreaming, motor output appropriate to the hallucinated motor activity in the dream occurs, but that this activity does not get through to the periphery. Marchiafava and Pompeiano[40] have shown that destruction of the sensory motor cortex or even the pyramids does not abolish the muscular twitches. Furthermore, movement, muscular contraction in response to stimulation of the motor cortex or the pyramidal tract, is virtually abolished during paradoxical sleep. In contrast, Hodes and Suzuki[41] have shown the motor cortex to be more excitable during this period. These physiological studies suggest that the twitches may represent something quite different from abortive motor activity accompanying dreaming. Dement, however, still wonders whether, in the normal cat, some of the movements during sleep are not associated with organized patterns of motor activity. He showed a slow-motion movie of a sleeping cat in which the movements appeared to be relatively coordinated and were reminiscent of leaps. In sleeping humans there are smiles, frowns, and other facial expressions. In women, pelvic thrusts occur, perhaps related to sexual dreams, while penile erections are common in males. Furthermore, detumescence has been reported by Fisher, Gross, and Zuch[42] as accompanying anxiety in dreams. Baust and his colleagues[43], and Dewson et al.[44] have shown that middle-ear muscles are active during the period of rapid eye movements. A number of investigators have reported heart-rate, respiratory, and blood-pressure changes during paradoxical sleep.[45] Some have associated lability of heart rate and apneic pauses with specific dream content. But it has proved difficult to correlate these with emotions reported in dreams.

It is not certain whether the motor pattern occurring during paradoxical sleep is associated with subjective experiences of dreaming. Dement, however, has stated that dream content is not necessarily dependent on peripheral events: the blind, the deaf, and amputees all have dreams involving experiences they cannot have had in the waking state. Money[46] has shown that paraplegics still experience dream orgasms although they are incapable of erection or ejaculation under control from higher centers. They can have similar vivid

sexual sensations during waking daydreams equally independent of events in the peripheral nervous system. A long series of studies does show, however, that sensory input, while not necessary for dreaming, can influence it, and a suppression of sensory activity is no longer believed to occur. There are now many studies of evoked responses recorded at the cortex during paradoxical sleep which apparently represent signals arriving over sensory pathways. These are difficult to interpret at the present time, and it is particularly difficult to say how closely the total pattern of afferent activity during different stages of sleep resembles that in the waking state.

Dement emphasized that although external stimuli during the REM period play some role in determining dream content, the most important factor is the character and content of the ideation preceding the REM period. It is possible to influence dream content by hypnotic suggestion, and Verdone and Rechtschaffen[29] have shown that the nearer the dream is to the initial bedtime, the more likely it is to be influenced by the previous day's experience.

Very little is known of the optimal conditions necessary for recall of dreams. It is possible that dreaming occurs in almost the entire period of paradoxical sleep even in people who never report dreams, but there is a defect in recall associated with sleeping. Rechtschaffen (unpublished) has suggested that this is possibly due to a failure to consolidate the memories of the subjective experiences of dreaming, analogous to the memory defect in the patients with bilateral hippocampal lesions of Milner.[47] Brown and Shryne[48] have shown that during slow-wave sleep the hippocampus seems to be isolated, judging by evoked potential recordings. Their results may support Rechtschaffen's hypothesis.

B. Experimental Studies of Responsiveness during Different Types of Sleep: H. L. Williams, I. Oswald, V. Rowland

The physiological studies of both orthodox and paradoxical sleep already discussed suggest that the patterns of organization of nervous system activity are very different from those in the waking brain. It would be very interesting to know how the brain changes in its capacity to process information in these various stages. One methodological problem, however, is that this capacity may differ not only with the stage of sleep, but may vary depending on the nature of the input, the type of task posed for the subject, and the response system used as an indicator. Dr. Williams, who has worked extensively on this problem, discussed several aspects

of responsiveness during sleep.

He began by reviewing what is known of the activity of the autonomic nervous system during the different stages of sleep. Autonomic physiologists customarily measure a number of variables that reflect the state of activity of the reticular formation, the hypothalamus, and those mechanisms that play upon them. These measures include heart rate, blood pressure, and respiratory rate, and their variability, as well as peripheral vascular constriction, and changes in skin potential and the capacity of the skin to conduct a small electric current (often used as an indirect measure of sweat gland activity). Most of these mechanisms are under the influence of both the parasympathetic and the sympathetic nervous systems. In the waking state, a high degree of arousal usually leads to increased heart rate, blood pressure, and respiratory rate, as well as increased skin conductance. Superimposed on this baseline is a set of spontaneous changes (occurring without specific external stimuli) sometimes interpreted as evidence of intermittent mentation with affective overtones. Of course, when events in the environment impinge on the subject, there are still other changes whose latency relationship to the afferent input can be interpreted as reactive. Although there are marked individual differences in the reactivity of different measures, on the whole, in the waking state these measures change together. Williams emphasized that these measures are useful for the study of reactivity in the different sleep states, although they are probably also related to the time of night and the phase in the circadian cycle.

We would expect the baseline measures to be lower during sleep, with less spontaneous activity, and less reactivity to environmental input. Experimental studies, however, do not support this expectation for every measure and, in fact, reveal a dissociation of the different measures. In deep sleep, associated with slow waves in the EEG, the heart rate, respiratory rate, and blood pressure are relatively low, and the peripheral vascular system is dilated, as would be expected. However, the number of spontaneous electrodermal responses is at a maximum. This is difficult if not impossible to explain by the usual argument that these changes reflect subjective mentation and/or anxiety. In paradoxical sleep, the baseline cardiovascular measures are higher than in orthodox sleep, as would be expected, and each burst of rapid eye movement is accompanied by constriction of the peripheral vascular system and by slight increases in breathing rate. However, the spontaneous activity of the skin practically disappears during

paradoxical sleep. This interesting dissociation requires further study and probably a revision of our interpretation of autonomic measures as indices of arousal even in the waking state.

An additional example of dissociation was given by Oswald, who has investigated two young men who bang their heads against their beds repeatedly during sleep. This behavior has been reported to occur mainly in orthodox sleep, but Oswald finds it can also occur during the paradoxical phase. Their heart rate failed to increase with head-banging and rocking during sleep, presumably in the paradoxical period, although ordinary non-rhythmic major movement interrupting sleep would always produce a marked rise. This suggests the existence of some type of "decoupling" of visceral control by the brain. This phenomenon also needs further study.

Williams described an experiment carried out by him, Dement and others (Williams, 1964) in which sleeping subjects were tested at different stages of sleep to see whether they could or would respond to an auditory signal by pressing a microswitch taped to the hand. The auditory signal varied in loudness from waking threshold in five-decibel steps. The louder the signal the greater was the percentage of signals to which a response was made. In stage II and stage III sleep, the increase in responsiveness with an increase in loudness of the signal was marked, although there were never responses to more than 30 percent of the signals. The responsiveness during both slow-wave, stage IV sleep and paradoxical sleep was less than for lighter sleep, as would be expected, and the increase in the percentage of responses, made with increasing loudness of the signal, created a much less steep slope. With this type of test, subjects respond just as infrequently in paradoxical sleep as in deep sleep for all levels of loudness of the signal. This finding corresponds to the observations of many investigators demonstrating that responsiveness of cats during paradoxical sleep is even less than during deep orthodox sleep.

Williams, however, pointed out that this unresponsiveness during paradoxical sleep is very dependent on the type of test situation. He described another study in which a tone was presented every 2 or 3 minutes to a sleeping subject who, when awake, had been told that he should press a switch when the tone was heard. (Williams, 1966) There were no immediate consequences if the subject did not respond. Under

these conditions the subjects responded about 80 percent of the time in very light sleep (stage I), and responded increasingly less as sleep became deeper. As in the previously reported experiment, the response rate during paradoxical sleep was just as poor as during deep sleep. However, if the experiment was changed so that there were dramatic consequences if the subject did not respond to the signal within 4 seconds (i.e., being awakened by a fire alarm, flashing lights, and electric shocks applied to the leg), the response rate to the same signal during paradoxical sleep was much higher, almost as high as during very light sleep. Responsiveness during deep sleep remained as poor as it was to the unconditional signal. Dement, among others, asked whether subjects tended to wake up slightly under these conditions. Williams pointed out that the definition of awakening is ambiguous, and that he cannot in any case be sure that there was no awakening. He did show that although some signs in the EEG suggested arousal, there was no evidence of alpha rhythm (characteristic of the waking EEG) in 70% of the trials; this suggests the subjects did not actually awaken.

Similar findings were obtained when subjects were asked to respond differentially to two signals, i.e., to discriminate between two tones, presented in random order, that differed in frequency but not loudness. One of the signals was neutral, while the other signal was negatively reinforced, that is, was followed by shocks or other noxious stimuli if no response was made. Very few responses were made to the neutral stimulus during any stage of sleep; however, the reinforced stimulus produced a high percentage of responses in light sleep, very few in deep orthodox sleep, and a good percentage during paradoxical sleep.

If the discrimination task is made more difficult, subjects again may show a failure to respond during paradoxical sleep. This may be because the discrimination of complex inputs cannot occur during paradoxical sleep, or it may be due to special features of the experiments. In one such complex discrimination study, the subject was supposed to discriminate between patterns of tones differing in pitch, presented in pairs sequentially in time. The failure to discriminate the differences between different sequences during paradoxical sleep may have been due to a failure to remember which tone came first.

Oswald added to this discussion of cognitive processes during sleep by presenting briefly a study in which he

exposed sleeping subjects to tape recordings of names, some spoken in the usual way and others "played backwards." He showed that subjects respond to forward names and not backward names. He used as a measure of response the presence of K-complexes in the EEG. (These long-lasting high-voltage biphasic waves, appear following stimulation of any sense modality.) (See page 14.)

Kleitman pointed out that, in some sense, paradoxical sleep in humans can be considered either light or deep depending on the nature of the task. If the subject is not concerned with the relevance of signals, he simply does not respond to them in paradoxical sleep. The difficulty lies in the concept of "relevance." It is very difficult to make clear in biological terms what makes some stimuli "relevant" and others not.

It should be stressed that although humans respond only to "relevant" stimuli during paradoxical sleep, this does not seem to be true for cats or, probably, for other animals. Clemente,[49] who has done careful studies of instrumental conditioning and discrimination in the cat, failed to demonstrate increased responsiveness occurring during paradoxical sleep. Possibly paradoxical sleep in cats differs in some respects from that in humans, with a much greater degree of decoupling of the nervous system from the environment; or perhaps in animals with simpler cognitive mechanisms it is relatively easier to interfere with discrimination mechanisms and render them inoperative.

The distinction made in this summary between physiological and psychological studies of sleep is inapplicable when both types of study are carried out simultaneously. We have referred to investigations as "psychological" when the primary emphasis has been either on subjective experience or on an input-output analysis of behavior. It is obvious that at the present time many workers are beginning studies that combine relatively complex investigations at the psychological level with simultaneous recording of physiological events.

Rowland reported on his studies of differential EEG arousal to conditioned auditory stimuli. A cat (prepared with chronically implanted electrodes to permit simultaneous EEG recording from multiple sites) was trained to associate one auditory cue with a subsequent shock and another cue with no such consistent effect. The influence of these two stimuli was compared in both waking and sleeping, using both EEG and behavioral criteria, giving the following results: A sleeping

animal, very early in training, shows both EEG and behavioral arousal to both signals, presumably because both signals are novel, and one is not uniquely associated with the shock. Later in training (when we assume conditioning has occurred), the animal shows minimal behavioral or EEG arousal to the neutral stimulus, but shows both to the shock-associated signal. Still later in training, the EEG may show arousal to the onset of the signal that is followed by shock, although the animal appears to remain asleep. These results demonstrate the dissociation between behavioral and EEG arousal and suggest that discrimination with behavioral consequences can occur without obvious simultaneous effects on behavior.

If the duration of the alerting signal associated with shock is prolonged up to 2 minutes, before the shock is actually delivered, a number of interesting phenomena are demonstrable. First, the EEG arousal, when it does occur, does not take place in all regions of the brain simultaneously. This is in agreement with the views already stated by Hess. Furthermore, some areas show some desynchronization with the onset of the signal but return to synchronization between alerting and a later arousal, occurring after one minute of signal associated with the increasing imminence of the shock. The anterior lateral gyrus, for instance, considered an association area, shows this phenomenon conspicuously, whereas the reticular formation and specific sensory areas do not show it so markedly. This phenomenon is influenced by shock intensity, with higher shock levels tending to eliminate the intervening synchrony.

Because it had been noted that neutral or control tones tended to intensify the EEG evidence of sleep, studies were carried out with a so-called safety signal. A continuous auditory signal was invariably followed by shock 2 minutes after its onset. But in some trials, an additional auditory signal (superimposed on the first during the desynchronization response of the second minute) indicated that shock would <u>not</u> follow, despite the continuation of the usual alerting signal. This "safety" signal produced a continuation of, or a return to sleep, by EEG criteria, suggesting that even in light sleep, presumably not paradoxical, the cat can discriminate such safety signals in association with transient EEG arousal, and behave differentially to them by arousing further or by returning to sleep depending on the presence or absence of shock reinforcement.

Rowland believes that satiation produced by ample feeding after food deprivation produces states analogous to sleep,

in that the differing effects of arousing signals on the ongoing EEG pattern in satiation and non-satiation resemble those in sleep (or drowsiness) and waking. He associates synchrony in the EEG with drive reduction whether in sleep or in satiation. Buchwald et al.[50] have shown synchrony during consummation response in the cat; this has been repeatedly observed in Rowland's laboratory. This position may be related to Pavlov's controversial view that sleep is due to irradiated inhibition; but in any case, the phenomenon of increased synchrony of the EEG in sleep and in satiated states needs explanation. Rowland and Evarts discussed different interpretations of the relationship between unit cell spikes and EEG synchrony. Some workers believe that the evoked response, occurring in the EEG is, in some sense, a histogram of unit discharges.[51] Evarts pointed out that this relationship cannot hold for all unit cells since some have activity patterns very different from others, and some are certainly behaving in a way that appears to be independent of the synchronization seen in the EEG. Rowland suggested that some cells are "independents" whose firing pattern can nonetheless be brought into synchrony or into an arousal pattern under the influence of hypnogenic or arousal factors, respectively.

Williams made another important observation. In recent years a great deal of interest has been focused on the capacity of the nervous system to respond during paradoxical sleep. It seems clear that in humans, whether stimuli are relevant or not, there is much reduced responsiveness during very deep sleep. It is still of interest, however, to know whether there is any responsiveness at all during this type of sleep. If the response is not recorded by a switch but by changes in the electrical activity in the thumb muscles, a response to an auditory signal presented to humans can still be noted. Thus, the influence of the environment does not disappear in the deepest sleep; the failure to obtain overt behavioral responses under these conditions may be due to an attenuation of the response so that it is not observable, rather than to the absence of the response in nervous system effector pathways. Physiological studies of the electrical activity of the nervous system in sleep show complex shifts in the pattern of neuronal activity. We need to know how these shifts influence psychological processes, although detailed correlations of this kind must wait for more information on the patterns of physiological activity in the nervous system.

C. Effects of Normal Sleep on Memory: K. M. Dallenbach

In the early studies of memory using nonsense syllables,

frequent use was made of the retention curve. This was a plot of the percent of nonsense syllables retained on retesting after various intervals had intervened following the original learning. This curve, of course, demonstrated a loss of retention with the passage of time, but also frequently contained hints that the slope of loss differed depending on whether the intervening time was spent sleeping or waking.

Dallenbach presented his classic work on the effect of sleep on retention, first published in 1924. Two student subjects memorized lists of ten nonsense syllables to the point of one correct recitation and were later asked to reproduce the list. The intervals between learning and retention were spent either in sleep or in waking activities. The retention scores were higher after sleep than after equal intervals of activity, and they were as high after 8 hours as after 2, provided the time was spent in sleep. Dallenbach drew the following conclusion: "The results of our study as a whole indicate that forgetting is not so much a matter of the decay of old impressions and associations as it is of the interference, inhibition, or obliteration of the old by the new." This study has been repeated many times and has provided the basis for studies testing the decay and interference hypothesis. This phenomenon is generally accepted at the present, but we still do not understand the effect of new learning on recently learned material at the physiological level.

V. THE PSYCHOLOGICAL PHENOMENOLOGY OF ABNORMAL STATES OF SLEEP AND WAKEFULNESS

A. States Produced by Manipulating Environmental Factors: H. L. Williams

A human subject, prevented from falling asleep by arousal at any sign of drowsy behavior, does not show a continuous decline in performance; rather, he has brief intermittent periods of poor performance surrounded by performance generally as good as baseline levels. Dr. Williams described the clinical picture of individuals after prolonged total sleep deprivation and, in addition, summarized his experimental studies designed to clarify the nature of the psychological deficit thus produced.

Intermittent lapses in performance after sleep deprivation have been noted by many observers. They were studied by Kleitman, and earlier by Bills,[52] who called them "blocks," while Liberson[53] called them "microsleeps." A sleep-deprived subject in a simple continuous performance task such as a vigilance experiment, shows brief interruptions of performance lasting a second or two. Very similar lapses in performance are also seen in chlorpromazine intoxication, in states of oxygen deprivation, under high nitrogen pressure, and in a number of other adverse environmental situations. At the present time there is no reason to believe that these phenomena all share a common physiological basis. These lapses, which occur after sleep deprivation, appear to be changes in the direction of light sleep. During such lapses, the subject's eyes develop a characteristic unfocused stare, his head drops forward, and his neck muscles relax. If he is brought sharply to arousal from one of these states in the early hours of sleep deprivation, he reports transient visual experiences. Later on, as the lapses increase in frequency, duration, and perhaps in depth, he is more likely to report more dream-like experiences. After the first night of sleep-loss, his eyes itch, and he complains of blurred vision and diplopia. After 48 hours of sleep loss he may report visual illusions, for example, the floor may look wavy, steam may seem to come from unexpected places, and small objects may appear to be crawling about. During this period the subject may be quite uncertain of the origin of these illusions, attributing them to his eyes, for instance. Some subjects, who go on to as many as 80 hours of sleep loss, show more or less clear-cut delusions, with no insight. Some subjects have been studied for very long periods of time, up to 250 hours of sleep deprivation. Their bizarre

behavior tends to occur on a diurnal circadian cycle in association with lapses. It is much worse during the early morning hours than later, when the subject would ordinarily be awake and working. The frequency of lapses is definitely associated with changes in temperature, since in the early morning hours there is definite evidence of lower temperature. West et al.[54] have concluded from their studies of one subject (on whom voluminous clinical records were made) that the difficulties in behavior seen in very long sleep deprivation occur on a 60- to 90-minute cycle. It is possible to predict the onset of a lapse by observing the EEG change quite suddenly from a waking record to a low-voltage record whose dominant frequency is about 5-6 per second. (This is similar to the EEG seen in the drowsy period before normal sleep.) The EEG then shifts back to the normal pattern just as abruptly. If the degree of constriction of the small vessels in the finger is measured, a transient constriction is followed by dilatation as the lapse begins, and is followed still later by constriction when the lapse is over. In some subjects, a shift in EEG frequency is highly correlated with lapses and therefore with deficits in performance. If, for instance, EEG frequency is under 7 per second, the reaction is either very delayed or absent because the subject misses the appropriate cue. There also is a clear-cut correlation between good performance test scores and EEG frequencies above 7 per second, and vice versa.

The nature of the performance deficit resulting from prolonged sleep deprivation depends on the nature of the experimental task. In a work-paced task (in which the time of stimulus presentation and the duration of the response interval is under the control of the experimenter), the subject is likely to show his deficit by errors of omission. On the other hand, in self-paced tasks, the deficit is shown by decreased speed of performance. In self-paced tasks, subjects probably are aware of their lapses and simply begin again, thus avoiding errors but increasing the time necessary to complete a task.

It is of considerable practical importance to know the effects of sleep deprivation on learning and memory. In addition, if reliable information can be obtained it might provide clues that would help in the investigation of the biological basis of memory. Unfortunately, it is extremely difficult to develop experimental techniques that are not open to certain criticism. For instance, most tests would be easier to interpret if we assumed all subjects start an experiment with the same baseline performance. Unfortunately, there are known to be marked individual differences in human learning ability and

in the amount of factual knowledge that each individual possesses which may help in new learning tasks. It is very difficult to find several tasks whose difficulty is accurately matched. Also, both motivation and attention, which play a powerful role in human learning, are difficult to control. Williams described these problems and then summarized some experiments which, while not avoiding all of these difficulties, nevertheless give some definite clues concerning the type of memory deficit that results from sleep deprivation.

In one experiment, Williams gave subjects items of factual information, then asked them to repeat the information back, some of it immediately and some of it after 24 hours. As sleep deprivation continued, there was an increasing deficit in the number of items retrieved, both immediately and after the delay. Since this could have been accounted for by the subjects' failure to understand fully the material, in a replication of the study, subjects were required to demonstrate that they understood the test items. Even in this second study there was difficulty with immediate recall and even greater difficulty with delayed recall. However, the effect on immediate recall occurred earlier in sleep loss than the effect on delayed recall. In other experiments, subjects were asked to tell stories they had heard once before. These stories were of approximately equal length with about 20 to 26 identifiable themes in each. There were two groups of stories, one set presented before sleep deprivation, and a second group presented one-a-day during sleep deprivation. Subjects recalled the group learned before sleep deprivation quite effectively throughout the experiment. The stories learned during sleep deprivation, on the other hand, were recalled with difficulty, and many items were lost even though they were requested immediately after they were told. A story presented the day after sleep was recalled effectively. In a similar experiment, stories like those just described were presented on one day and recall was attempted 24 hours later throughout a period of sleep deprivation. The amount of recall decreased throughout the experiment. The important point is that recall of the last story, learned after sleep deprivation had ended, was still very poor. This was in contrast to that part of the other experiment in which stories learned before sleep deprivation were recalled well after it, or those learned after recovery were recalled on the same day as described. All of these studies strongly suggest that the earliest difficulty produced by sleep deprivation is one of acquisition, not of retrieval or recovery from storage.

B. Drug-Induced States that Show Certain Similarities to Naturally Occurring States of Sleep and Wakefulness: I. Oswald

For many years drugs have been used to produce and prevent sleep. The mode of action of these drugs is not well understood, but in recent years combined studies by physiologists and pharmacologists have suggested possible mechanisms of action. Several hypotheses have been discussed earlier in this report. (See pp. 26-30.) In addition to physiological studies, clinical investigations often suggest useful ideas, and sometimes even a single case carefully studied suggests hypotheses that could not be derived from experiments because the experiments cannot be carried out ethically on human subjects. Dr. Oswald presented clinical data on cases of human subjects under the influence of drugs, and following withdrawal of drugs before and after some adaptation to prolonged use had occurred.

Under normal conditions, approximately 20 percent of the night's sleep is of the paradoxical type, very little of which is in the first two hours. Oswald cited the work of Rectschaffen and Maron[55] on amphetamine, which increases the amount of orthodox sleep at the expense of paradoxical sleep, and produces insomnia or artificial wakefulness. Barbiturates appear to produce orthodox sleep directly. Oswald reports that mixtures of the two drugs also produce this phenomenon. However, if individuals take these drugs regularly over long periods of time and develop tolerance to them, the ratio of orthodox and paradoxical sleep returns to a normal range.

Oswald reported on his studies of patients who had been addicted to a mixture of amobarbital and dextroamphetamine. When these drugs are stopped, after a period of prolonged use during which tolerance has developed, the percentage of paradoxical sleep is increased markedly and it occurs earlier in the sleep period. This is not due to prior paradoxical sleep deprivation because these individuals show normal orthodox-to-paradoxical ratios before the drugs are stopped. Dement raised the possibility that it might be very difficult to ascertain their state of deprivation, since after paradoxical sleep deprivation the need for extra paradoxical sleep can be delayed for long periods before it is finally made up.

Oswald also reported the case of a man who was chronically addicted to large amounts of Tranylcypromine (Parnate), a monoamine oxidase inhibitor. For some time he had been

taking up to 70 pills a day on his own initiative, because of the euphoric effect they produced. While taking the drug he sometimes showed no paradoxical sleep whatever and also showed a curious muscle artifact in his EEG records. When the drug was finally withheld effectively, he had difficulty falling asleep (in this he differed from amphetamine addicts), but when he did go to sleep he went directly into paradoxical sleep, spending up to 75% of the night in this state. This percentage is very unusual. In addition, each night, as the patient went into paradoxical sleep, he had a frightening dream.

Experimental subjects who took "Mogadon" (nitrazepam), or amobarbital sleeping pills showed a suppression of paradoxical sleep when first taking the drugs, with the percentage returning to normal after several days. On withdrawal from the drugs, the percent of the night spent in paradoxical sleep rose above normal and slowly returned. Dr. Jarvik noted that the increase in paradoxical sleep began quite soon after stopping the drug; this surprised him, since Librium, a chemically related drug, is excreted quite slowly.

Levotryptophan produces a drowsy state in animals. Oswald found that, given by mouth to human subjects in a dose of 5 to 10 grams per night, it produced a pressure toward earlier paradoxical sleep and an increased percentage of paradoxical sleep. He studied the effects of this drug in several subjects who showed the phenomenon to a high degree compared to several different controls. Lactose, levo-tyrosine and methionine, by contrast, produced no effect.

One route of tryptophan metabolism is to 5-hydroxytryptophan and thence to 5-hydroxytryptamine. The drug methysergide has a very potent and specific blocking effect upon the action of 5-hydroxytryptamine. When Oswald's normal subjects were pre-treated with methysergide for three days, tryptophan no longer had its former effect upon sleep. Further experiments showed that patients with idiopathic narcolepsy were particularly sensitive to the tryptophan, which caused a large increase in the period of paradoxical sleep occurring in them at sleep onset. This suggests that a tryptophan - 5-hydroxytryptophan mechanism is involved in producing paradoxical sleep. Oswald raised the interesting possibility that the amount of certain biogenic amines present in the nervous system could account for the switching from one sleep stage to another.

C. Effects of Somnolence- and Stimulation- Producing Drugs on Learning and Memory: M. Jarvik

There is now a very large literature on the effect of drugs on learning and memory. Dr. Jarvik reviewed some of this work, and in particular, outlined a series of his own experiments. In this report we shall discuss only those issues that have a direct bearing on sleep and wakefulness. Although many drugs appear to produce sleepiness, in most cases the state differs in definite ways from naturally occurring sleep and drowsiness. Effects of drugs on performance may, of course, be based either on those effects that are similar to sleep or on totally different mechanisms. Great caution must be used, therefore, in drawing inferences concerning sleep from drug studies, and vice versa.

Drugs that tend to produce somnolence could either impair or enhance performance; they could act on the learning itself, the period of retention or storage, or the recovery process. Since the test of memory is always the retrieval of the stored information, it is difficult to separate effects on the three stages. Often indirect reasoning must be used. Also, since all studies of learning and memory use performance of some kind as a measure, one must decide whether the drug affects learning, retention, or recall, on the one hand, or performance itself, on the other.

Drugs producing somnolence or impaired consciousness could act to enhance recall by preventing the effects on a memory trace of intervening environmental stimuli. This effect would be the exact analogue of the phenomenon discovered by Dallenbach. Summerfield and Steinberg[56] have presented data on the effects of nitrous oxide anesthesia on human subjects: those subjects who received the anesthetic after learning showed greater recovery of learned material than those in an awake control group.

Drugs producing somnolence or impaired consciousness could also act by interfering with the consolidation of the memory trace. In this case, drugs administered during the interval between learning and recall would impair performance if given right after learning, but would not necessarily do so if given later. Jarvik presented data from his own studies and from others that suggest that some drugs act in this way.[57]

A number of investigators have shown that drugs usually regarded as stimulants may enhance performance of animals in

certain types of learning tasks. For instance McGaugh and Petrinovich[57] have shown that strychnine and picrotoxin improve performance of maze-learning in rats. At the present time there is very little evidence that such stimulant drugs act on any sleep-wakefulness mechanism to produce their results, unless, by simply preventing sleep, they make effective learning possible. These studies have been extensively reviewed by the above authors.

BLANK PAGE

VI. EPILOGUE

Although the Work Session was brief and included relatively few participants, it nonetheless yielded a vast amount of new information and clearly indicated the directions of contemporary sleep research. A good portion of the data presented centered on the phenomenology of sleep, the changes in activity of an organism's various functional systems which characterize sleep and allow a distinction to made between waking and sleep, and, of equal importance, between various phases or stages of sleep. Many of the data presented stressed qualitative differences between "old-fashioned" orthodox or slow-wave sleep (including its various EEG stages) on the one hand, and "new" paradoxical, activated or low-voltage fast sleep on the other. To the unbiased observer, our Work Session (as well as present-day sleep research in general) may seem to stress activated sleep excessively at the expense of classical slow-wave sleep. Whether justified or not, this intensive preoccupation with paradoxical sleep has, in the last few years, greatly enriched our knowledge of the dreaming stage of sleep so that by now we certainly know at least as much about fast-wave sleep as we do about slow-wave sleep.

Since much that was assumed to be common knowledge by participants in our Work Session may not be familiar to the less specialized reader, it may be useful in this section to present in tabular form some functional differences between slow-wave sleep, fast-wave sleep, and wakefulness, and also to point out some striking differences among the various phases as they occur in the two most-often-studied species, man and cat. (See Fig. 12.) It becomes evident, as subjects shift from waking to slow-wave sleep and paradoxical sleep, that some functional changes in activity are parallel in man and cat; other functional units, however, reveal divergent, indeed often opposite changes, a fact suggesting that fast-wave sleep in man may be a very different functional state from what it is in cats. The work of many investigators suggests that paradoxical sleep is a kind of "endpoint." To cite an example from Evarts' work, a continuous increase or decrease in discharge frequency of the large and small neurons, respectively, takes place with the transition from waking to slow-wave sleep and paradoxical sleep. An interesting tendency towards "vollying" also occurs. In addition, the evidence for "uncoupling," that functional detachment of the various brain stem and cortical mechanisms from the motoneuronal level, is strongest in paradoxical sleep. This

Indicator	Waking	CAT Slow-Wave Sleep	CAT Fast-Wave Sleep	MAN Slow-Wave Sleep	MAN Fast-Wave Sleep
Cortical EEG	alpha waves or fast (arousal) pattern	sleep spindles and/or slow waves	fast (arousal) pattern	same as in cat	same as in cat
Hippocampal EEG	fast activity	high voltage spikes	theta (4-7) waves	N.A.	N.A.
Mesencephalic Reticular Formation	fast activity	slow waves	fast activity	N.A.	N.A.
Lateral Geniculate	inconspicuous fast-slow wave pattern	inconspicuous fast-slow wave pattern	spikes	N.A.	N.A.
Evoked Potentials	usually increasing in amplitude with shift from waking to slow-wave sleep to fast-wave sleep			not well established; latency prolonged; amplitude possibly decreased	not well established; latency close to waking; amplitude possibly decreased
Reflexes (tendon)	normal	slightly decreased	profoundly diminished	same as in cat	same as in cat
Eye Movements	related to particular activity	none or slow	REM's	same as in cat	same as in cat
Muscles	activity related to momentary activity	somewhat relaxed	atonia all over except for limb, trunk and face twitches	same as in cat	same as in cat
Heart Rate	related to momen- activity	somewhat lowered	considerably lowered but phasic increases	decreased	increased close to waking
Blood Pressure	related to momentary activity	somewhat lowered	considerably lowered but phasic increases and drops	decreased	increased close to waking
Respiration	related to momentary activity	decreased	decreased irregular	same as in cat	same as in cat
Pupils	related to level of attention, light, etc.	miosis	miosis	same as in cat	same as in cat
Nictitating Membrane	contracted in cat	relaxed	relaxed	N.A.	N.A.
Threshold for Arousal, Attention & Orienting Response	low	increased	highly increased	depending on test situation: increased	depending on test situation: increased or decreased as compared with slow-wave sleep

Figure 12. Some functional differences between slow-wave sleep and fast-wave sleep in cat and man as compared with waking.

interpretation is not incompatible with the findings of Candia et al.[58] who report that, in the cat, blood pressure drops to a minimum during paradoxical sleep; moreover, Candia, as well as Hodes and Suzuki[41] and Jouvet[59] find that the arousal threshold is considerably higher in paradoxical sleep than during either slow-wave sleep or waking. Winters[60], on the other hand, assumes that paradoxical sleep is, rather, a transitional phase between waking and (slow-wave) sleep. From the findings of Shagass and Trusty[61], who measured the latency of various components of sensory evoked potentials in man during the different stages of sleep, one likewise is led to conclude that paradoxical sleep is a state intermediate between stages I and II.

Quite apart from the light they shed on the spectrum of levels of vigilance, studies such as Evarts' are of considerable value in providing information about central nervous mechanisms during sleep in general. An essential finding reported from such studies is that, during sleep, the brain is not quiescent and that, in fact, many units, particularly larger neurons, are more active during sleep than during waking. These studies also have shown that the neuronal activities characteristic, respectively, of waking, sleeping and the various sleep stages, can be more qualitative than quantitative both with respect to single units and to populations. Of course, it will be necessary to ascertain whether the populations studied by Evarts (visual and motor cortex) and by Huttenlocher[5] (reticular formation) have activity cycles representative of the whole brain. A study of the frontal cortex -- which, according to Piéron[62] is the only brain region showing histological damage after prolonged sleep deprivation -- would be of particular interest. Such future work may yet uncover evidence that certain "super cells" in the brain indeed <u>do</u> sleep during sleep.

Dr. Hess' comprehensive discussion of the EEG signs of sleep does not call for many additional comments. Since its introduction into the bio-medical field, the EEG has been an invaluable diagnostic corollary to the various stages of sleep, although at times overly strict adherence to the classical EEG signs of sleep may have inhibited progress. With the natural restraint of careful investigators, Hess, Koella and Akert wrote in 1953:[63] "... one may note the absence of sleep potentials when the cat seems to sleep;" they did not dare at that time to accept an EEG activation pattern as an alternative manifestation of sleep and, along with many others, missed their chance to recognize paradoxical

sleep. Of particular interest in Hess' presentation was the discussion of some more episodic sleep signs, such as sharp vertex waves, and especially the K-complex signs, which may eventually provide insight into the more fundamental sleep mechanisms. Grey Walter[64] has suggested that the K-complex may be the manifestation of some "sleep-protecting" mechanism, which thus could be classified as the expression of a kind of negative feedback process. Roth's[65] observation that rhythmically recurring K-complexes still appear for a few seconds after a repetitive (auditory) stimulus is stopped, would indicate that the organism "anticipates" continuation of the rhythmical stimulus and (if the Grey Walter's interpretation is correct) that it tends to counteract the potentially arousing effect of these stimuli by means of an inhibitory or anti-arousal discharge. In general, however, so long as little is known about the fundamental processes underlying the EEG wave forms encountered in the various stages of the sleep-vigilance cycle, EEG signs will continue to provide little more than pragmatic criteria by which to distinguish those stages.

For similar reasons, it is still too early to attempt a more detailed interpretation of the EEG manifestations of paradoxical sleep. It has been suggested that in this particular stage of sleep the cerebral cortex is activated, a state conceivably related to the high degree of mental activity occurring during dreaming. On the other hand, it has been shown recently with a careful computer technique that the EEG of paradoxical sleep, though at first glance similar to that of activated waking, differs from the latter in important respects.[66]

A similar situation pertains with respect to the steady or ultraslow potentials recorded from the surface as well as from subcortical sites of the brain during the various states of vigilance. Rowland has already pointed to the various difficulties in technique and interpretation. As in the case of the EEG (which may be interpreted, in part, as a modulation of the steady potential), the fundamental difficulty lies in our current ignorance of the source of these d-c potentials. Recently, W. H. Marshall (personal communication) has suggested that the steady EMF's (electromotive forces) may be a manifestation of a blood-brain barrier (BBB) potential; if this is true, their fluctuation with the state of vigilance may signal changes in the permeability of the BBB. It is to be hoped that future research will clarify this very fundamental question.

Rossi initiated the discussion of neural mechanisms of sleep. By distinguishing between passive and active sleep mechanisms, he clearly indicated that sleep is not merely "de-waking" or "de-arousal," but requires certain additional active processes to bring about some of its underlying somatic and visceral functional states. Thus, Rossi aligned himself with the evident majority of the participants (and, for that matter, of most of today's sleep investigators) who see sleep as an actively induced and controlled phenomenon. This view is based largely on phenomenological evidence, although the initial and often-repeated observation of Hess that sleep can be induced by electrical stimulation of certain brain areas, has done much to strengthen it. The stimulation experiments are, however, still ambiguous to some extent. The regions from which various investigators have elicited sleep are numerous; they include the cerebral cortex,[67] the hippocampus,[68] the thalamus,[69,70,71,72] the anterior hypothalamus and preoptic area,[73] the midbrain and pontine reticular formation,[74,75] medullary structures,[76] and peripheral nerves.[26,77] The last-mentioned findings, particularly, suggest the possibility that low-rate stimulation per se is a sleep-inducing agent, possibly via Pavlov's internal inhibitory mechanisms[78] and that the locus of stimulation is rather irrelevant. In fact, the only locus from which a sleep-like picture can be induced by high-rate as well as by low-rate stimulation is, according to Sterman and Clemente,[73] the preoptic area. Yet, the sleep (or sleep-like) effects produced from the various structures mentioned above reveal some striking qualitative and temporal differences which strongly suggest that some locus specificity nevertheless exists. For example, cats stimulated in the midline thalamus (intralaminal nuclei) first exhibit characteristic "presomnic" behavior (including circling movements, prone position, folded forepaws, slow lid and pupil closure), and only fall asleep after this initial phase; they often stay asleep for periods of six to eight hours, often exhibiting phases of fast-wave, low-voltage sleep. Stimulation of the preoptic area, the midbrain reticular formation, the medullary nucleus of the solitary tract and the peripheral nerves, by contrast, induces a sleep pattern that is usually not preceded by a phase of presomnic symptoms and does not outlast stimulation to the same extent. Stimulation of the hippocampal structures induces mainly presomnic effects,[68] whereas stimulation of the caudal pontine reticular formation induces paradoxical sleep with a background of slow-wave sleep. It thus seems possible that the intralaminar thalamic structure constitutes the main and highest coordinating sleep structure, whereas

other hypnotropic areas subserve only subfunctions within the whole phenomenon of sleep. This notion is supported by Jouvet's observation[75] (1963, and present report) that destruction of the caudal part of the pontine reticular formation eliminates paradoxical sleep while leaving slow-wave sleep undisturbed, and by the observation of Sterman et al.[79] that, in the cat, lesions in the basal forebrain reduce the time spent in the drowsy state and increase the total waking time but leave the actual sleeping time unchanged.

Hernández-Peón's report was of considerable interest, not only because it further indicated the structures involved in the control of sleep, but also because it suggested the nature of the nervous transmitter substance operating at synaptic junctions interspersed in the sleep-controlling apparatus. Hernández-Peón's findings, furthermore, brought evidence concerning the direction of the "information flow" in this apparatus. In view of the importance of these findings, it is somewhat surprising that his experiments so far have not been repeated by others. Several aspects of his technique invite further study, in particular the concentration gradient (which probably decreases proportional to the square of the distance from the crystal), the penetration coefficient, and the specificity of the neuronal reactions to the various (distance-dependent) concentrations of the drug. Nonetheless, Hernandez-Péon's technique not only has contributed substantially to our understanding of the central sleep mechanisms, but it also may prove to be of great value in investigations of problems other than sleep.

The report by Koella likewise concerned central nervous humoral agents, but placed particular emphasis on sleep-inducing factors. The classical work by Piéron,[62] later repeated and in part confirmed by Schnedorf and Ivy,[80] as well as the newer findings by Kornmüller et al.[81] and by Monnier et al.[82] strongly indicates the existence of hypnogenic factors of a humoral nature. Koella's results suggest that serotonin may be among such agents.

Kety's discussion of biogenic amines stressed the evident functional relation of amines of the catechol type to arousal or the waking state. The short description of the effects of gamma hydroxybutyric acid touched also on the problem of humoral sleep-inducing factors. It should be mentioned, however, that besides the somewhat conflicting reports as to the existence of this compound in the brain,[15, 16] Winters and Spooner[83] have reported it to be an epilepto-

genic rather than a hypnogenic agent. More research will be needed to ascertain whether this interesting compound is indeed a biogenic agent.

One aspect of sleep control was not discussed at any length, namely, feedback mechanisms. It may seem futile to attempt a "systems analysis" of sleep at a time when control of sleep is still little understood and the notion of its active nature is not yet fully accepted. Nevertheless, some aspects of sleep, particularly its time course, suggest the the existence of feedback mechanisms. Moruzzi, in a recent article[78] suggests a kind of positive feedback system operating between the effector periphery (i.e., the muscles) and the reticular core of the brain stem, an arrangement which would well explain the relatively rapid transition from wakefulness to (deep) sleep. Koella[84] suggests the existence of a positive feedback loop between the hypnogenic zone of the thalamus and the arousal component of the reticular formation. The K-complex, which has been interpreted as a manifestation of sleep-protecting (i.e., homeostatic or negative feedback) mechanism, was mentioned in the foregoing account.

Much of the Work Session was concerned with the psychological aspects of sleep. Nothing need be added to the informative accounts of Dement, Williams, Oswald, Rowland, Dallenbach and Jarvik, except, perhaps, a note on the reports of sleep-deprivation studies. This topic was touched upon not only by the psychology-oriented participants, but also by Jouvet. There was consensus that sleep deprivation leads to malperformance, the severity of which depends upon the nature of the experimental task and the extent of deprivation, but the potential value of sleep deprivation experiments in elucidating the functional role of sleep was not discussed at any length. Indeed, as was already briefly mentioned in the Overview, very little is known at present about the physiological functions of sleep. Some investigators have suggested that sleep may be a kind of retreat, that a certain amount of dreaming is necessary for the mental welfare of the subject, and that the main functional role of sleep should be defined in psychological rather than in physiological terms. It is easy to detect some "sense" in many functional manifestations of sleep, particularly if one does not shy away from teleologically guided considerations. For example, the narrow pupil, the active closure of the eyelids and the active inhibition of the spinal motoneurons, resulting in a suspension of all reflexively and supraspinally induced motor output, all seem to act toward one goal, namely, the avoidance

of premature arousal. These three phenomena, together with many others, could be interpreted as but auxiliary somatic changes, protecting sleep but in themselves irrelevant to those still unknown processes that constitute the ultimate functional role of sleep.

At the conclusion of this report, a brief consideration of the outlook of sleep research may be appropriate. Judging from the recent literature on sleep, as well as from the presentations at this Work Session, it seems that most investigators are concerned primarily with the phenomenology of sleep. Undeniably, this interest in uncovering more and more sleep symptoms, in analyzing sleep patterns, and in studying differences in sleep characteristics among the various species, has led to a rapid expansion of knowledge of the total phenomenon of sleep. Future research will undoubtedly add numerous further details. Extrapolating from current achievements, we may look forward to the time when we shall know how sleep affects the cellular and even the subcellular componentry of all major organ systems. Useful as such information would be, however, it would still leave major central problems unexplored. The virtually complete lack of knowledge about the fundamental functional role of sleep - that it probably serves to provide restitution for some of the central, at least, and possibly also of peripheral neurons - should prompt additional inquiries along other lines. Hydén's[85] recent finding that during sleep the succinoxydase activity in nerve cells of the brain-stem reticular formation is markedly elevated compared with this activity in the waking state, and that the reverse is true of neighboring glia cells, appears as a promising first step towards an understanding of the more basic aspects of sleep. One may hope that biochemistry-oriented investigators will undertake more systematic studies of cell populations from many different regions of the brain (including, in particular, the frontal cortex) and will extend their efforts over a variety of biochemical processes which may relate to the restitutional function of sleep, hitherto only vaguely established.

Another problem demanding intensified research concerns the neural mechanisms controlling sleep. Several promising beginnings were reported at our Work Session: at least some central nervous system areas that appear to be involved in the induction, maintenance and termination of sleep have been delineated by stimulation and elimination experiments. The recent work of the Pisa laboratory[86] on the spinal reflexes, Evarts' study on pyramidal cells of the motor cortex, and the

older work of W.R. Hess[10] on the pupil, to name only a few, have identified some of the intermediate control mechanisms governing the peripheral activity changes characteristic of the sleep-wakefulness cycle. The work by Piéron,[62] Kornmüller[81] Monnier,[82] Hernández-Peón,[87] Bessman et al.,[15] and Koella,[88] has begun to elucidate humoral factors which may play a role either as para- or tele-transmitters in the control of sleep. Much work lies ahead, however, and it will unquestionably require a combined effort by neurophysiologists, neuroanatomists, neurochemists, neuropharmacologists, and systems engineers to establish the identity and the logic of the nervous and humoral mechanisms that comprise the complex functional system governing the induction, maintenance and termination of that mysterious state in which man spends one-third of his lifetime.

Works Cited

1. Loomis, A.L., Harvey E.N. and Hobart, G.A. (1937): Cerebral states during sleep, as studied by human brain potentials. J. Exp. Psychol. 21:127-144.

2. Gibbs, E.L. and Gibbs, F.A. (1947): Diagnostic and localizing value of electroencephalographic studies in sleep. Res. Publ. Assn. Nerv. Dis. 26:366-376.

3. Jasper, H.H. (1958): Recent advances in our understanding of ascending activities of the reticular system. In: Reticular Formation of the Brain. Jasper, H.H., Proctor, L.D., Knighton, R.S., Noshay, W.C. and Costello, R.T., eds. Boston: Little, Brown, Pp. 319-331.

4. Hubel, D.H. (1959): Single unit activity in striate cortex of unrestrained cats. J. Physiol. 147:226-238.

5. Huttenlocher, P.R. (1961): Evoked and spontaneous activity in single units of medial brain stem during natural sleep and waking. J. Neurophysiol. 24:251-268.

6. Caspers, H. (1961): Changes of cortical d.c. potentials in the sleep-wakefulness cycle. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churchill, Pp. 237-253.

7. Kawamura, H. and Sawyer, C.H. (1964): D-C potential changes in rabbit brain during slow-wave and paradoxical sleep. Amer. J. Physiol. 207:1379-1386.

8. Wurtz, R.H. (1965): Steady potential shifts in the rat during desynchronized sleep. Electroenceph. Clin. Neurophysiol. 19:521-523.

Wurtz, R.H. (1965): Steady potential shifts during arousal and deep sleep in the cat. Electroenceph. Clin. Neurophysiol. 18:649-662.

9. Sherrington, C. (1947): The Integrative Action of the Nervous System. 2nd ed. New Haven: Yale University Press.

10. Hess, W.R. (1924, 1925): Über die Wechselbeziehungen zwischen psychischen und vegetativen Funktionen. Schweiz. Arch. Neurol. Psychiat. 15:260-277; 16:36-55, 285-306.

11. Lübbers, D.W., Ingvar, D., Betz, E., Fabel, H., Kessler, M. and Schmahl, F.W. (1964): Sauerstoff verbrauch der Grosshirnrinde in Schlaf- und Wochzustand beim Hund. Pflügers Archiv. f.d. ges. Physiol. 281.

12. Birzis, L. and Tachibana, S. (1964): Local cerebral impedance and blood flow during sleep and arousal. Exper. Neurol. 9:269-285.

13. Kanzow, E. (1965): Changes in blood flow of the cerebral cortex and other changes during paradoxical sleep periods in the unrestrained cat. In: Aspects Anatomo-Functionnels de la Physiologie du Someil, CNRS (Paris)

14. Wolf, J.P. (1960): The Florey Factor I. In: Inhibition in the Nervous System and Gamma-Aminobutyric Acid. Roberts, E., ed. New York: Pergamon, Pp. 416-417.

15. Bessman, S.P. and Fishbein, W.N. (1963): Gamma-hydroxybutyrate, a normal brain metabolite. Nature 200:1207-1208.

16. Giarman, N.J. and Roth, R.H. (1964): Differential estimation of gamma-butyrolactone and gamma-hydroxybutyric acid in rat blood and brain. Science 145:583-584.

17. Laborit, H., Jouany, J., Gerard, J. and Fabiani, F. (1960): Sur un substrat métabolique. Action centrale inhibitrice. Le 4-hydroxybutyrate de Na. La Presse Med. 68: 1867-1869.

18. Glowinski, J. and Axelrod, J. (1965): The effect of drugs in the uptake, release and metabolism of H^3 norepinephrine in the rat brain. J. Pharmacol. 149:43-49.

19. Scheving, L.E. (1964): Temporal variations in the susceptibility of white rats to pentobarbital sodium and tremorine. Int. J. Neurophysiol. 3:651-658.

20. Davis, W.M. (1962): Day-night periodicity in pentobarbital response of mice and the influence of socio-psychological conditions. Experientia 18:235-237.

21. Wooley, D.E. and Timiras, P.S. (1962): Estrous and circadian periodicity and electro-shock convulsions in rats. Amer. J. Physiol. 202:379-382.

22. Harner, R.N. and Halberg, F. (1958): Electrocortiograph differences in D_8 mice at times of daily high and low susceptibility to audiogenic convulsions. Physiologist 1:34-35.

23. Batini, C., Moruzzi, G., Palestini, M., Rossi, G.F. and Zanchetti, A. (1959): Effects of complete transections on the sleep-wakefulness rhythm: the midpontine pretrigeminal preparation. Arch. Ital. Biol. 97:1-12.

24. Magnes, J., Moruzzi, G. and Pompeiano, O. (1961): Synchronization of the EEG produced by low-frequency electrical stimulation of the region of the solitary tract. Arch. Ital. Biol. 99:33-67.

25. Dell, P., Bonvallet, M. and Hugelin, A. (1961): Mechanisms of reticular deactivation. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor M., eds. London: Churchill, Pp. 82-102.

26. Pompeiano, O. and Swett, J.E. (1962): Identification of cutaneous and muscular afferent fibres producing EEG synchronization or arousal in normal cats. Arch. Ital. Biol. 100:343-380.

27. Moruzzi, G. (1962): Active processes in the brain stem during sleeping. In: The Harvey Lectures, Series 58. New York: Academic, Pp. 233-297.

28. Clemente, C.D., Sutin, J. and Silverstone, J.T. (1957): Changes in electrical activity of the medulla on the intravenous injection of hypertonic solutions. Amer. J. Physiol. 188:193-198.

29. Rechtschaffen, A., Verdone, P. and Wheaton, J. (1963): Reports of mental activity during sleep. Canad. Psychiat. J. 8:409-414.

30. Foulkes, W. (1962): Dream reports from different stages of sleep. J. Abnorm. Soc. Psychol. 65:14-25.

31. Kamiya, J. (1961): Behavioral, subjective, and physiological aspects of drowsiness, and sleep. In: Functions of Varied Experience. Riske, D.W. and Maddi, S.R., eds. Homewood, Illinois: Dorsey Press.

32. Goodenough, D., Shapiro, A., Holden, M. and Steinschriber, L. (1959): A comparison of "dreamers" and "non-dreamers":

eye movements, electroencephalograms, and the recall of dreams. J. Abnorm. Soc. Psychol. 59:295-302.

33. Jeannerod, M. and Mouret, J. (1962): Etude des mouvements oculaires observés chez l'homme au cours de la veille et du sommeil. C.R. Soc. Biol. (Paris) 156:1407.

34. Deckert, G. (1964): Pursuit eye movements in the absence of a moving visual stimulus. Science 143:1192-1193.

35. Brady, J. and Levitt, E. (1964): Nystagmus as a criterion of hypnotically induced visual hallucinations. Science 146:85-86.

36. Offenkrantz, W. and Wolpert, E. (1963): The detection of dreaming in congenitally blind subjects. J. Nerv. Ment. Dis. 136:88-90.

37. Amadeo, M. and Gomez, E. (1964): Eye movements and dreaming in subjects with life-long blindness. (Presented at 4th Annual Meeting of the Association for the Psychophysiological Study of Sleep, Palo Alto, California, March, 1964.)

38. Jeannerod, M., Mouret, J. and Jouvet, M. (1965): Etude de la phase paradoxale du sommeil chez le chat. Electroenceph. Clin. Neurophysiol. 18:554-566.

39. Berlucchi, G., Moruzzi, G., Salvi, G. and Strata, P. (1964): Pupil behavior and ocular movements during synchronized sleep. Arch. Ital. Biol. 102:230-244.

40. Marchiafava, P. and Pompeiano, O. (1964): Pyramidal influences on spinal cord during desynchronized sleep. Arch. Ital. Biol. 102:500-529.

41. Hodes, R. and Suzuki, J. (1965): Comparative thresholds of cortex, vestibular system and reticular formation in wakefulness, sleep and rapid eye movement periods. Electroenceph. Clin. Neurophysiol. 18:239-249.

42. Fisher, C., Gross, J. and Zuch, J. (1965): Cycle of penile erection synchronous with dreaming (REM) sleep. Arch. Gen. Psychiat. 12:29-45.

43. Baust, W., Berlucchi, G. and Moruzzi, G. (1964): Changes in the auditory input in wakefulness and during the synchronized and desynchronized stages of sleep. Arch.

Ital. Biol. 102:637-674.

44. Dewson, J., Dement, W. and Simmons, F. (1965): Observations on middle ear muscle activity during sleep in cat. J. Exp. Neurol. 12:1-8.

45. Verdone, P. (1965): Temporal reference of manifest dream content. Percept. Mot. Skills 20:1253-1268.

46. Money, J. (1961): Sex hormones and other variables in human eroticism. In: Sex and Internal Secretions. Young, W.C., ed. Baltimore: Williams and Wilkins.

47. Milner, B. (1959): The memory defect in bilateral hippocampal lesions. Psychiat. Res. Rep. 11:43-52.

48. Brown, B. and Shryne, J. (1966): EEG theta activity and fast activity sleep in cats as related to behavioral traits. Neuropsychologie (In press)

49. Clemente, C.D. and Sterman, M.B. (1963): Cortical synchronization and sleep patterns in acute restrained and chronic behaving cats induced by basal forebrain stimulation. Electroenceph. Clin. Neurophysiol. Suppl. 24:172-187.

50. Buchwald, N.A., Horvath, F.E., Wyers, E.J. and Wakefield, C. (1964): Electroencephalogram rhythms correlated with milk reinforcement in cat. Nature 201:830.

51. Fox, S.S. (1965): Duplication of evoked potential waveform by curve of probability of firing of a single cell. Science 147:888.

52. Bills, A.G. (1931): Blocking: A new prinicple of mental fatigue. Amer. J. Physiol. 43:230-245.

53. Liberson, W.T. (1945): Problem of sleep and mental disease. Dig. Neurol. Psychiat. 13.

54. West, L.J., Janszen, H., Lester, B.K. and Cornelison, F.S. (1962): The psychosis of sleep deprivation. In: Biological Aspects of Schizophrenic Behavior. Sanker, S., Conf. ed. Ann. N.Y. Acad. Sci. 96:66-70.

55. Rechtschaffen, A. and Maron, L. (1964): Effect of amphetamine on the sleep cycle. Electroenceph. Clin. Neurophysiol. 16:438-444.

56. Summerfield, A. and Steinberg, H. (1957): Reducing interference in forgetting. Quart. J. Exp. Psychol. 9:146-154.

57. McGaugh, J. and Petrinovich, L.F. (1965): Effects of drugs on learning and memory. Int. Rev. Neurobiol. 8: 139-196.

58. Candia, O., Favale, E., Giussani, A. and Rossi, G.F. (1962): Blood pressure during natural sleep and during sleep induced by electrical stimulation of the brain stem reticular formation. Arch. Ital. Biol. 100:216-233.

59. Jouvet, M. (1962): Recherches sur les structures nerveuses et les mécanismes responsables des differentes phases du sommeil physiologique. Arch. Ital Biol. 100:125-206.

Jouvet, M. (1963): The rhombencephalic phase of sleep. In: Brain Mechanisms. (Progress in Brain Research, Vol. 1) Moruzzi, G., Fessard, A. and Jasper, H.H., eds. Amsterdam: Elsevier, Pp. 407-424.

Jouvet, M. and Jouvet, D. (1963): A study of the neurophysiological mechanisms of dreaming. Electroenceph. Clin. Neurophysiol. Suppl. 24:133-157.

Jouvet, M. (1965): Étude de la dualité des états de sommeil et des mécanismes de la phase paradoxale. Éditions du Centre Nat. de la Recherche Scientifique. 127:397-449.

60. Winters, W.D. (1964): Comparison of the average cortical and subcortical evoked response to clicks during various stages of wakefulness, slow wave sleep and rhombencephalic sleep. Electroenceph. Clin. Neurophysiol. 17:234-245.

61. Shagass, S. and Trusty, D.M. (1966): Somatosensory and visual cerebral evoked response changes during sleep. In: Recent Advances in Biological Psychiatry, 8. Wortis, J , ed. New York: Plenum (In press)

62 Piéron, H. (1913): Le Problème Physiologique du Sommeil. Paris: Masson.

63. Hess, R., Koella, W.P. and Akert, K. (1953): Cortical and subcortical recordings in naturally and artificially

induced sleep in cats. Electroenceph. Clin. Neurophysiol. 5:75-90.

64. Walter, W. Grey (1953): The Living Brain. London: Duckworth.

Walter, W. Grey (1954): Theoretical properties of diffuse projection systems in relation to behaviour and consciousness. In: Brain Mechanisms and Consciousness. Delafresnaye, J.F., ed. Springfield: C. C Thomas.

65. Roth, R.H., Shaw, J. and Green, J. (1956): The form, voltage distribution and physiological significance of the K complex. Electroenceph. Clin. Neurophysiol. 8:385-402.

66. Kiyono, S. and Iwama, K. (1965): Frequency spectra of the cortical EEG's in wakefulness-sleep cycle of cats with special reference to paradoxical phase of sleep. Jap. J. Physiol. 15:366-377.

67. Penaloza-Rojas, J.H., Elterman, M. and Olmos, N. (1964): Sleep induced by cortical stimulation. Exp. Neurol. 10: 140-147.

68. Parmeggiani, P.L. (1962): Sleep behaviour elicited by electrical stimulation of cortical and subcortical structures in the cat. Helv. Physiol. Acta 20:347-367.

69. Hess, W.R. (1944): Hypothalamische Adynamie. Helv. Physiol. Acta 2:137-147.

Hess, W.R. (1944): Das Schlafsyndrom als Folge dienzephaler Reizung. Helv. Physiol. Acta 2:305-344.

70. Akert, K., Koella, W.P. and Hess, R. (1952): Sleep produced by electrical stimulation of the thalamus. Amer. J. Physiol. 168:260-267.

71. Jouvet, M. (1962): Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch. Ital. Biol. 100:125-206.

72. Akimoto, H., Yamaguchi, W., Okatse, K., Nakagawa, T., Nakamura, I., Abe, K., Takii, H. and Masahashi, K. (1956): On the sleep induced through electrical stimulation on dog thalamus. Folia Psychiat. Neurol. 10:117-146.

73. Sterman, M.B. and Clemente, C.D. (1962): Forebrain inhibitory mechanisms: cortical synchronization induced by basal forebrain stimulation. Exp. Neurol. 6:91-102.

Sterman, M.B. and Clemente, C.D. (1962): Forebrain inhibitory mechanisms: sleep patterns induced by basal forebrain stimulation in the behaving cat. Exp. Neurol. 6: 103-117.

74. Flavale, E., Loeb, C., Rossi, G.F. and Sacco, G. (1961): EEG synchronization and behavioral signs of sleep following low frequency stimulation of the brainstem reticular formation. Arch. Ital Biol. 99:1-22.

75. Jouvet, M. (1963): The rhombencephalic phase of sleep. In: Brain Mechanisms. (Progress in Brain Research, Vol. 1) Moruzzi, G., Fessard, A. and Jasper, H.H., eds. Amsterdam: Elsevier, Pp. 407-424.

Jouvet, M. and Jouvet, D. (1963): A study of the neurophysiological mechanisms of dreaming. Electroenceph. Clin. Neurophysiol. Suppl. 24:133-157.

76. Magnes, J., Moruzzi, G. and Pompeiano, O. (1961): EEG synchronization from medullary structures. Fed. Proc. 20:336.

77. Pompeiano, B. and Swett, J.E. (1962): EEG and behavioral manifestations of sleep induced by cutaneous nerve stimulation in normal cats. Arch. Ital. Biol. 100:311-342.

78. Moruzzi, G. (1960): Synchronizing influences of the brainstem and the inhibitory mechanisms underlying the production of sleep by sensory stimulation. Electroenceph. Clin. Neurophysiol. Suppl. 13:231-256.

79. Sterman, M.B., Krauss, T.K., Lehmann, D. and Clemente, C.D. (1964): Alterations of sleep patterns following basal lesions. Fed. Proc. 23:209.

80. Schnedorf, J.G. and Ivy, A.C. (1939): An examination of the hypnotoxin theory of sleep. Amer. J. Physiol. 125: 491-505.

81. Kornmüller, A.E., Lux, H.D., Winkel, K. and Klee, M. (1961): Neurohumoral ausgelöste Schlafzustände an Tieren

mitgekreuztem Kreislauf unter der Kontrolle von EEG - Ableitungen. Naturwissenschaften 48:503-505.

82. Monnier, M., Koller, Th. and Graber, S. (1963): Humoral influences of induced sleep and arousal upon electrical brain activity of animals with crossed circulation. Exp. Neurol. 8:264-277.

83. Winters, W.D. and Spooner, C.E. (1965): A neurophysiological comparison of gamma-hydroxybutyrate with pentobarbital in cats. Electroenceph. Clin. Neurophysiol. 18: 287-296.

84. Koella, W.P. (1966): Sleep: Its Nature and Physiological Organization. Springfield: C. C Thomas. (In press)

85. Hydén, H. and Lange, P.W. (1964): Rhythmic enzyme changes in neurons and glia during sleep and wakefulness. Life Sci. 3:1215-1219.

86. Giaquinto, S., Pompeiano, O. and Somogyi, I. (1963): Reflex activity of extensor and flexor muscles following muscular afferent excitation during sleep and wakefulness. Experientia 19:481-482.

Giaquinto, S., Pompeiano, O. and Somogyi, I. (1963): Supraspinal inhibitory control of spinal reflexes during natural sleep. Experientia 19:652-653.

Giaquinto, S., Pompeiano, O. and Somogyi, I. (1964): Descending inhibitory influences on spinal reflexes during natural sleep. Arch. Ital. Biol. 102:282-307.

87. Hernández-Peón, R. (1965): Central neuro-humoral transmission in sleep and wakefulness. In: Sleep Mechanisms. (Progress in Brain Research, Vol. 18) Akert, K., Bally, C. and Schadé, J.P., eds. Amsterdam: Elsevier, Pp. 96-117.

88. Koella, W.P., Trunca, C.M. and Czicman, J.S. (1965): Serotonin: effect on recruiting responses of the cat. Life Sci. 4:173-181.

RELEVANT PUBLICATIONS OF PARTICIPANTS

Karl M. Dallenbach

Glanville, A.D. and Dallenbach, K.M. (1920): The range of attention. Amer. J. Psychol. 41:202-236.

Jenkins, J.G. and Dallenbach, K.M. (1924): Obliviscence during sleep and waking. Amer. J. Psychol. 35:605-612.

Guilford, J.P. and Dallenbach, K.M. (1925): The determination of memory span by the method of constant stimuli. Amer. J. Psychol. 36:621-628.

Minami, H. and Dallenbach, K.M. (1946): The effect of activity upon learning and retention in the cockroach. Amer. J. Psychol. 59:1-58.

William Dement

Dement, W. and Kleitman, N. (1957a): Cyclic variations in EEG during sleep and their relation to eye movements, body motility and dreaming. Electroenceph. Clin. Neurophysiol. 9:673-790.

Dement, W. and Kleitman, N. (1957b): The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. J. Exp. Psychol. 53:339-346.

Dement, W. (1958): The occurrence of low voltage, fast, electroencephalogram patterns during behavioral sleep in the cat. Electroenceph. Clin. Neurophysiol. 10:291-296.

Dement, W. and Wolpert, E. (1958): The relation of eye movements, body motility, and external stimuli to dream content. J. Exp. Psychol. 55:543-553.

Dement, W. and Wolpert, E. (1958): Relationships in the manifest content of dreams occurring on the same night. J. Nerv. Ment. Dis. 126:568-578.

Dement, W. (1960): The effect of dream deprivation. Science 131:1705-1707.

Roffwarg, H., Dement, W., Muzio, J. and Fisher, C. (1962): Dream imagery: relationship to rapid eye movements of sleep.

Arch. Gen. Psychiat. 7:235-258.

Kahn, E., Dement, W., Fisher, C. and Barmack, J. (1962): Incidence of color in immediately recalled dreams. Science 137: 1054-1055.

Rechtschaffen, A., Wolpert, E., Dement, W., Mitchell, S. and Fisher, C. (1963): Nocturnal sleep of narcoleptics. Electroenceph. Clin. Neurophysiol. 15:599-609.

Dement, W. (1964): Experimental dream studies. In: Science and Psychoanalysis, Vol. VII. Masserman, J., ed. New York: Grune and Stratton.

Antrobus, J., Dement, W. and Fisher, C. (1964): Patterns of dreaming recall: an EEG study. J. Abnorm. Soc. Psychol. 69:341-344.

Williams, H., Hammack, J., Daly, R., Dement, W. and Lubin, A. (1964): Responses to auditory stimulation, sleep loss and the EEG stages of sleep. Electroenceph. Clin. Neurophysiol. 16:269-279.

Dement, W. (1965): An essay on dreams: The role of physiology in understanding their nature. In: New Directions in Psychology, II. New York: Holt, Rinehart & Winston, Pp. 137-257.

Dement, W. (1965): Recent studies on the biological role of rapid eye movement sleep. Amer. J. Psychiat. 122:404-408.

Dement, W., Rechtschaffen, A. and Gulevich, G. (1966): The nature of the narcoleptic sleep attack. Neurology 16:18-33.

Dement, W. (1966): Sleep and dreams. In: American Handbook of Psychiatry, Vol. III. Arieti, S., ed. New York: Basic Books, (In press)

Dement, W., Henry, P., Cohen, H. and Ferguson, J. (1966): Studies on the effect of REM deprivation in humans and in animals. Proc. Assoc. Res. Nerv. Ment. Dis. (In press)

Roffwarg, H., Muzio, J. and Dement, W. (1966): The ontogenetic development of the sleep-dream cycle in the human. Science 152:604-619.

See also Williams, H.L.

Edward V. Evarts

Evarts, E.V. and Magoun, H.W. (1957): Some characteristics of cortical recruiting responses in unanesthetized cats. Science 125:1147-1148.

Fleming, T.C., Huttenlocher, P.R. and Evarts, E.V. (1959): Effect of sleep and arousal on the cortical response to lateral geniculate stimulation. Fed. Proc. 46:347.

Evarts, E.V., Fleming, T.C. and Huttenlocher, P.R. (1960): Recovery cycle of visual cortex of the awake and sleeping cat. Amer. J. Physiol. 199:373-376.

Evarts, E.V. (1960a): Effects of sleep and waking on spontaneous and evoked discharges of single units in visual cortex. Fed. Proc. 19:828-837.

Evarts, E.V. (1960b): Spontaneous and evoked activity of single units in visual cortex of cat during sleep and waking. Fed. Proc. 19:290.

Evarts, E.V. (1961): Effects of sleep and waking on activity of single units in the unrestrained cat. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churchill, Pp. 171-182.

Evarts, E.V. (1962): Activity of neurons in visual cortex of cat during sleep with low voltage fast EEG activity. Fed. Proc. 21:351B.

Evarts, E.V., Bental, E., Bihari, B. and Huttenlocher, P.R. (1962): Spontaneous discharges of single neurons during sleep and waking. Science 135:726-728.

Evarts, E.V. (1963): Photically evoked responses in visual cortex units during sleep and waking. J. Neurophysiol. 26: 229-248.

Evarts, E.V. (1964): Temporal patterns of discharge of pyramidal tract neurons during sleep and waking in the monkey. J. Neurophysiol. 27:152-171.

Franz Halberg

Halberg, F., Engel, R., Halberg, E. and Gully, R.J. (1952): Diurnal variations in amount of electroencephalographic

paroxysmal discharge and diurnal eosinophil rhythm of epileptics on days with clinical seizures. Fed. Proc. 11: 63.

Halberg, F. (1953): Some physiological and clinical aspects of 24-hour periodicity. Lancet 73:20-32.

Halberg, F., Bittner, J.J., Gully, R.J., Albrecht, P.G. and Brackney, E.L. (1955): 24-hour periodicity and audiogenic convulsions in I mice of various ages. Proc. Soc. Exper. Biol. Med. 88:169-173.

Halberg, F., Jacobsen, E., Wadsworth, G. and Bittner, J.J. (1958): Audiogenic abnormality spectra, 24-hour periodicity and lighting. Science 128:657-658.

Halberg, F. (1959): Physiologic 24-hour periodicity: general and procedural considerations with reference to the adrenal cycle. Z. Vitam.-Hormon.-Ferment Forsch. 10:225-296.

Halberg, F., Halberg, E., Barnum, C.P. and Bittner, J.J. (1959): Physiologic 24-hour periodicity in human beings and mice, the lighting regimen and daily routine. In: Photoperiodism and Related Phenomena in Plants and Animals. Withrow, R.B., ed. Washington, D.C.: A.A.A.S., Pp. 803-878.

Halberg, F., Peterson, R.E. and Silber, R.H. (1959): Phase relations of 24-hour periodicity in blood corticosterone, mitosis in cortical adrenal parenchyma and total body activity. Endocrinology 64:222-230.

Halberg, F. (1960): The 24-hour scale: a time dimension of adaptive functional organization. Perspect. Biol. Med. 3: 491-527.

Halberg, F. (1963): Circadian (about 24-hour) rhythms in experimental medicine. Proc. Roy. Soc. Med. 56:253-256.

Halberg, F. (1964): Organisms as circadian systems; temporal analysis of the physiologic and pathologic responses, including injury and death. In: Walter Reed Army Institute of Research Symposium, Medical Aspects of Stress in the Military Climate, April 1964, Pp. 1-36.

Halberg, F., Panofsky, H., Diffley, M., Stein, M. and Adkins, G. (1964): Computer techniques in the study of biologic rhythms. Ann. N.Y. Acad. Sci. 15:695-720.

Halberg, F., Siffre, M., Engeli, M., Hillman, D. and Reinberg, A. (1965): Etude en libre-cours des rythmes circadiens du pouls de l'alternance veille-sommeil et de l'estimation du temps pendant les deux mois de sejour souterrain d'un homme adulte jeune. C.R. Acad. Sci. (Paris) 260:1259-1262.

Halberg, F., Engeli, M., Hamburger, C. and Hillman, D. (1965): Spectral resolution of low-frequency, small-amplitude rhythms in excreted ketosteroid; probable androgen-induced circaseptan desynchronization. Acta Endocrinol. Suppl. 103: 1-54.

Haus, E. and Halberg, F. (1966): Circadian phase diagrams of oral temperature and urinary functions in a healthy man studied longitudinally. Acta Endocrinol. 51:215-223.

Reinberg, A., Halberg, F., Ghata, J. and Siffre, M. (1966): Spectre thérmique (rythmes de la température rectale) d'une femme adulte saine avant, pendant et aprés son isolement souterrain de trois mois. C.R. Acad. Sci. (Paris) 262:782-785.

Raul Hernández-Peón

Hernández-Peón, R., Lavin, A., Alcocer-Cuarón, C. and Marcelin, J.P. (1960): Activity of the olfactory bulb during wakefulness and sleep. Electroenceph. Clin. Neurophysiol. 12:41-58.

Hernández-Peón, R. (1962): Sleep induced by localized electrical or chemical stimulation of the forebrain. Electroenceph. Clin. Neurophysiol. 14:423-424.

Hernández-Peón, R., Chavez-Ibarra, G., Morgane, P.J. and Timo-Iaria, C. (1962): Cholinergic pathways for sleep, alertness and rage in the limbic midbrain circuit. Acta Neurol. Latinoamer. 8:93-96.

Hernández-Peón, R., Chavez-Ibarra, G., Morgane, P.J. and Timo-Iaria, C. (1963): Limbic cholinergic pathways involved in sleep and emotional behavior. Exp. Neurol. 8:93-111.

Velluti, R. and Hernández-Peón, R. (1963): Atropine blockade within a cholinergic hypnogenic circuit. Exp. Neurol. 8: 20-29.

Hernández-Peón, R. and Chavez-Ibarra, G. (1963): Sleep induced by localized electrical or chemical stimulation of the forebrain. In: The Physiological Basis of Mental Activity. Hernandez-Peon, R., ed. Electroenceph. Clin. Neurophysiol. Suppl. 24:188-198.

Hernández-Peón, R. (1964): Neurophysiological mechanisms of wakefulness and sleep. Acta Neurol. Latinoamer. 10:18-34.

Hernández-Peón, R. (1964): Attention, sleep, motivation and behavior. In: The Role of Pleasure in Behavior. Heath, R.G., ed. New York: Hoeber, Pp. 195-217.

Hernández-Peón, R. (1964): Neurophysiological correlates of EEG patterns during wakefulness and sleep. Electroenceph. Clin. Neurophysiol. 17:469-445.

Hernández-Peón, R. (1964): A cholinergic hypnogenic limbic forebrain-hindbrain circuit. Electroenceph. Clin. Neurophysiol. 17:444-445.

Hernández-Peón, R. (1965): Central neuro-humoral transmission in sleep and wakefulness. In: Sleep Mechanisms. (Progress in Brain Research, Vol. 18) Akert, K., Bally, C. and Schadé, J.P., eds. Amsterdam: Elsevier, Pp. 96-117.

Hernández-Peón, R. (1965): Behavioral and electrophysiological effects produced by cholinergic and adrenergic stimulation of the central nervous system. Excerpta Med. 99:106.

Hernández-Peón, R. (1965): Waking and sleeping patterns of brain activity and their relations to EEG. Abst. EEG Seccond Advanced Course in Electroencephalography. Pp. 21-22.

Hernández-Peón, R. (1965): A cholinergic hypnogenic forebrain-hindbrain circuit. In: Neurophysiologie des états du sommeil. Jouvet, M., ed. C.N.R.S. 127:63-88.

Hernández-Peón, R. (1965): Neural systems in the brain stem involved in wakefulness, sleep, and conscious experience. Excerpta Med. 93:123-124.

Hernández-Peón, R., O'Flaherty, J.J. and Mazzuchelli-O'Flaherty, A.L. (1965): Modifications of tactile evoked potentials at trigeminal sensory nucleus during wakefulness and sleep. Exp. Neurol. 13:40-57.

Mazzuchelli-O'Flaherty, A.L., O'Flaherty, J.J. and Hernández-Peón, R. (1966): Sleep and other behavioral responses induced by acetylcholinic stimulation of frontal and medial cortex. Brain Research (In press)

Rudolf Hess

Hess, R. (1964): The EEG in sleep. Electroenceph. Clin. Neurophysiol. 16:44-55.

Hess, R. (1966): Der paradoxale Schlaf. Forschritte der Medizin (In press)

Scollo-Lavizzari, G., Hess, R. and Guggenheim, P. (1966): Hirnelektrische Reizantworten im Schlaf. Schweiz. Archiv. für Neurologie, Neurochirurgie Psychiatrie (In press)

See also Koella, W.P.

Murray E. Jarvik

Jarvik, M.E., Abramson, H.A. and Hirsch, M.W. (1955): Lysergic acid diethylamide (LSD-25). IV. Effect on attention-concentration. J. Psychol. 39:373-383.

Jarvik, M.E. and Carley, J.L. (1964): A simple circuit for contact responses. J. Exp. Anal. Behav. 7:82.

Jarvik, M.E. (1964): The influence of drugs upon memory. In: CIBA Foundation Symposium on Animal Behavior and Drug Action. Steinberg, H., de Reuck, A.V.S. and Knight, J., eds. London: Churchill, Pp. 44-61.

Barondes, S. H. and Jarvik, M.E. (1964): The influence of actinomycin-D on brain RNA synthesis and on memory. J. Neurochem. 11:187-195.

Barron, F., Jarvik, M.E. and Bunnell, S. (1964): The hallucinogenic drugs. Sci. Amer. 210:28-37.

Berryman, R., Cumming, W., Nevin, J.A. and Jarvik, M.E. (1964): Effects of sodium pentobarbital on complex operant discriminations. Psychopharmacologia 6:388-398.

Michael Jouvet

Jouvet, M. (1961): Telencephalic and rhombencephalic sleep in the cat. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churchill, Pp. 188-206.

Jouvet, M. (1962): Recherches sur les structures nerveuses et les mécanismes responsables des différentes phases du sommeil physiologique. Arch. Ital. Biol. 100:125-206.

Jouvet, M. (1963): Aspects anatomo-fonctionnels de la physiologie du sommeil. Coll. Internat. C.N.R.S. N°127, Pp. 397-449.

Jouvet, M. (1963): The rhombencephalic phase of sleep. In: Brain Mechanisms. (Progress in Brain Research, Vol. 1) Moruzzi, G., Fessard, A. and Jasper, H.H., eds. Amsterdam: Elsevier, Pp. 406-424.

Jouvet, M. and Jouvet, D. (1963): A study of the neurophysiological mechanisms of dreaming. Electroenceph. Clin. Neurophysiol. 15:133-157.

Valatx, J.L., Jouvet, D. and Jouvet, M. (1964): Evolution électrocéphalographique des différents états de sommeil chez le chaton. Electroenceph. Clin. Neurophysiol. 17:218-233.

Jouvet, M. (1965): Paradoxical sleep - a study of its nature and mechanisms. In: Sleep Mechanisms. (Progress in Brain Research, Vol. 18) Akert, K., Bally, C. and Schadé, J.P., eds. Amsterdam: Elsevier, Pp. 20-62.

Jouvet, M. (1965): Behavioural and EEG effects of paradoxical sleep deprivation in the cat. Excerpta Medica Internat. Congr. Series n°87, Proc. XXIIIrd Internat. Congr. Physiol. Sci. Pp. 344-353.

Jouvet, M. (1965): Etude électrophysiologique et neuropharmacologique des des états de sommeil. Actualités Pharmacol. 18ème serie:109-173.

Jouvet, M. and Delorme, F. (1965): Locus coeruleus et sommeil paradoxal. C.R. Soc. Biol. (Paris) 159:895.

Jouvet, M., Vimont, P. and Delorme, F. (1965): Suppression élective du sommeil paradoxal chez le chat par les inhibiteurs de la monoamineoxydase. C.R. Soc. Biol. (Paris) 159:1595.

Delorme, F., Jeannerod, M. and Jouvet, M. (1965): Effets remarquables de la Réserpine sur l'activité EEG phasique ponto-geniculo-occipitale. C.R. Soc. Biol. (Paris) 159: 900.

Jeannerod, M., Mouret, J. and Jouvet, M. (1965): Etude de la motricité oculaire au cours de la phase paradoxale du sommeil chez le chat. Electroenceph. Clin. Neurophysiol. 18:554-566.

Seymour S. Kety

Mangold, R., Sokoloff, L., Conner, E., Kleinerman, J., Therman, P.G. and Kety, S.S. (1955): The effects of sleep and lack of sleep on the cerebral circulation and metabolism of normal young men. J. Clin. Invest. 34:1092-1100.

Kety, S.S. (1957): The general metabolism of the brain in vivo. In: Metabolism of the Nervous System. Richter, D., ed. London: Pergamon, Pp. 221-237.

Kety, S.S. (1961): Sleep and the energy metabolism of the brain. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churhill, Pp. 375-381.

Nathaniel Kleitman

Kleitman, N. (1961): The nature of dreaming. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churchill, Pp. 349-374.

Kleitman, N. (1963): Sleep and Wakefulness. rev. ed. Chicago: University of Chicago Press.

See also Dement, W.

Werner P. Koella

Hess, R., Akert, K. and Koella, W.P. (1950): Les potentiels bioélectriques du cortex et du thalamus et leur altération

par stimulation du centre hypnique chez le chat. Rev. Neurol. 83:537-544.

Akert, K., Koella, W.P. and Hess, R. (1952): Sleep produced by electrical stimulation of the thalamus. Amer. J. Physiol. 168:260-267.

Hess, R., Koella, W.P. and Akert, K. (1952): Cortical and subcortical recordings in unanaesthetized cats. Electroenceph. Clin. Neurophysiol. 4:370-371.

Hess, R., Koella, W.P. and Akert, K. (1953): Cortical and subcortical recordings in natural and artificially induced sleep in cats. Electroenceph. Clin. Neurophysiol. 5:75-90.

Koella, W.P. and Ballin, H.M. (1954): The influence of environmental and body temperature on the electroencephalogram in the anesthetized cat. Arch. Int. Physiol. 62:369-380.

Gellhorn, E., Koella, W.P. and Ballin, H.M. (1954): Interaction on cerebral cortex of acoustic or photic with nociceptive impulses: the problem of consciousness. J. Neurophysiol. 17:14-21.

Nakao, H. and Koella, W.P. (1956): Influence of nociceptive stimuli on evoked subcortical and cortical potentials in the cat. J. Neurophysiol. 19:187-195.

Koella, W.P., Smythies, J.R., Bull, D.M. and Levy, C.K. (1960): Physiological fractionation of the effect of serotonin on evoked potentials. Amer. J. Physiol. 198:205-212.

Koella, W.P., Smythies, J.R., Levy, C.K. and Czicman, J.S. (1960): Modulatory influence on cerebral cortical optic response from the carotid sinus area. Amer. J. Physiol. 199:381-386.

Koella, W.P. and Schaeppi, U. (1962): The reaction of the isolated cat iris to serotonin. J. Pharmacol. Exp. Therap. 138:154-158.

Koella, W.P. and Czicman, J.S. (1963): Influence of serotonin upon optic evoked potentials, EEG, and blood pressure of cat. Amer. J. Physiol. 204:873-880.

Koella, W.P. and Ferry, A. (1963): Cortico-subcortical homeostasis in the cat's brain. Science 142:586-589.

Koella, W.P., Trunca, C.M. and Czicman, J.S. (1965): Serotonin: effect on recruiting responses of the cat. Life Sci. 4: 173-181.

Koella, W.P. (1966): The central nervous control of sleep. In: The Hypothalamus. Haymaker, W.E., Anderson, P.J. and Nauta, W.J.H., eds. Springfield, Illinois: C. C Thomas. (In press)

Koella, W.P. and Czicman, J. (1966): The mechanism of the EEG-synchronizing action of serotonin. Amer. J. Physiol. (In press)

Koella, W.P. (1966): Sleep: Its Nature and Physiological Organization. Springfield, Illinois: C. C Thomas. (In press)

See also Hess, R.

Walle J. H. Nauta

Nauta, W.J.H. (1946): Hypothalamic regulation of sleep in rats. An experimental study. J. Neurophysiol. 9:285-316.

Nauta, W.J.H. (1958): Hippocampal projections and related neural pathways to the mid-brain in the cat. Brain 81:319-340.

Hubel, D.H. and Nauta, W.J.H. (1960): Electrocorticograms of cats with chronic lesions of the rostral mesencephalic tegmentum. Fed. Proc. 19:287.

Ian Oswald

Oswald, I., Taylor, A. and Treisman, M. (1960): Discriminative response to stimulation during human sleep. Brain 83:440-453.

Oswald, I. (1962): Sleeping and Waking: Physiology and Psychology. Amsterdam: Elsevier.

Oswald, I. (1962): Sleep mechanisms; recent advances. Proc. Roy. Soc. Med. 55:910-912.

Berger, R.J., Olley, P. and Oswald, I. (1962): The EEG, eye movements and dreams of the blind. Quart. J. Exp. Psychol. 14:183-186.

Berger, R.J. and Oswald, I. (1962): Effects of sleep deprivation on behavior, subsequent sleep and dreaming. J. Ment. Sci. 108:457-465.

Berger, R.J. and Oswald, I. (1962): Eye movements during active and passive dreams. Science 137:601.

Oswald, I., Berger, R.J., Jaramillo, R.A., Keddie, K.M.G., Olley, R.C. and Plunkett, G.B. (1963): Melancholia and barbiturates: a controlled EEG, body and eye movement study of sleep. Brit. J. Psychiat. 109:66-78.

Oswald, I. and Thacore, V.R. (1963): Amphetamine and phenmetrazine addiction: physiological abnormalities in the abstinence syndrome. Brit. Med. J. 2:427-431.

Oswald, I. (1964): Physiology of sleep accompanying dreaming. In: The Scientific Basis of Medicine Annual Reviews, 1964. Ross, J.P., ed. London: University of London Press.

Oswald, I., Ashcroft, G.W., Eccleston, D.G., Evans, J.I., Le Gassicke, J. and Ritson, B. (1965): The clinical state, nocturnal sleep and amine metabolism of a tranylcypromine (Parnate) addict. Brit. J. Psychiat. 111:357-364.

Oswald, I. and Priest, R.G. (1965): Five weeks to escape the sleeping pill habit. Brit. Med. J. 2:1093-1095.

Oswald, I. (1966): Sleep. Harmondsworth: Penguin.

Oswald, I., Ashcroft, G.W., Berger, R.J., Eccleston, D., Evans, J.I. and Thacore, V.R. (1966): Some experiments in the chemistry of normal sleep. Brit. J. Psychiat. 112:401-404.

Evans, J.I. and Oswald, I. (1966): Some experiments in the chemistry of narcoleptic sleep. Brit. J. Psychiat. 112: 391-400.

Gian Franco Rossi

Brodal, A. and Rossi, G.F. (1955): Ascending fibres in the brain stem reticular formation of cat. Arch. Neurol. Psychiat. 74:68-87.

Roger, A., Rossi, G.F. and Zinandoli, A. (1956): Le rôle des afférences des nerfs crâniens dans le maintien de l'état vigile de la préparation "encéphale isolé." Electroenceph. Clin. Neurophysiol. 8:1-13.

Batini, C., Moruzzi, G., Palestini, M., Rossi, G.F. and Zanchetti, A. (1959): Effects of complete transections on the

sleep-wakefulness rhythm: the midpontine pretrigeminal preparation. Arch. Ital. Biol. 97:1-12.

Rossi, G.F. (1961): Expériences sur l'importance du tron cérébral dans le mécanisme neurogene du comportement émotif. La Vie Medicale. Numéro spécial.

Rossi, G.F., Favale, E., Hara, T., Giussani, A. and Sacco, G. (1961): Researches on the nervous mechanisms underlying deep sleep in the cat. Arch. Ital. Biol. 99:270-292.

Pisano, M., Rosadini, G. and Rossi, G.F. (1962): Risposte corticali evocate da stimoli dromici ed antidromici durante il sonno e la veglia. Riv. Neurobiol. 8:414-426.

Rossi, G.F. (1963): Sleep inducing mechanisms in the brain stem. Electroenceph. Clin. Neurophysiol. Suppl. 24:113-132.

Rossi, G.F. (1963): A study of the signs of sleep in the cat. In: Brain Mechanisms. (Progress in Brain Research, Vol. 1) Moruzzi, G., Fessard, A. and Jasper, H.H., eds. Amsterdam: Elsevier, Pp. 404-406.

Palestini, M., Pisano, M., Rosadini, G. and Rossi, G.F. (1963): Studio dell'eccitabilita corticale durante il sonno e la veglia: ciclo di eccitabilita della corteccia visiva del gatto. Boll. Soc. Ital. Biol. Sper. 9:17-30.

Rossi, G.F. (1964): A hypothesis on the neural basis of consciousness. Acta Neurochir. 12:187-197.

Alema', G., Rosadini, G., Rossi, G.F. and Zattoni, J. (1964): Effetti clinici ed elettroencefalografici della somministrazione di amobarbital sodium del circolo vertebro-basilare dell'uomo. Boll. Soc. Ital. Biol. Sper. 40:835-838.

Di Paola, M., Pisano, M. and Rossi, G.F. (1964): Effetti ipnogeni della stimolazione elettrica della corteccia sensitivo-motrice del gatto. Boll. Soc. Ital. Biol. Sper. 40: 833-835.

Gentilomo, A., Rosadini, G., Rossi, G.F. and Zattoni, J. (1964): Modificazioni respiratorie, cardiocircolatorie e pupillari da inattivazione barbiturica del tronco encefalico. Boll. Soc. Ital. Biol. Sper. 40:843-845.

Palestini, M., Pisano, M., Rosadini, G. and Rossi, G.F. (1964): Visual cortical response evoked by stimulating lateral

geniculate body and optic radiations in awake and sleeping cats. Exp. Neurol. 9:17-30.

Rosadini, G., Gentilomo, A., Alema', G. and Rossi, G.F. (1964): Effetti neurologici ed elettroencefalografici dell'iniezione diretta di un barbiturico nel circolo vertebro-basilare del coniglio. Boll. Soc. Ital. Biol. Sper. 40:838-840.

Sekino, T., Candia, O. and Rossi, G.F. (1964): Effetti di lesioni mezencefaliche unilaterali sull'attivita elettroencefalografica del sonno profondo del gatto. Boll. Soc. Ital. Biol. Sper. 40:843-845.

Rossi, G.F. (1965): Brain stem facilitating influences on EEG synchronization. Experimental findings and observations in man. Acta Neurochim. 13:257-288.

Rossi, G.F. (1965): Some aspects of the functional organization of the brain stem: neurophysiological and neurosurgical observations. Excerpta Medica International Congress Series 93:117-122.

Rossi, G.F., Palestini, M., Pisano, M. and Rosadini, G. (1965): An experimental study of the cortical inactivity during sleep and wakefulness. In: Aspects anatomo-functionnels de la physiologie du sommeil. Coll. Internat. C.N.R.S. N°127, Pp. 509-526.

De Paola, M., Rossi, G.F. and Zattoni, J. (1965): Induction of EEG desynchronized sleep by electrical stimulation of the neocortex. Arch. Ital. Biol. 103:818-831.

Palestini, M., Pisano, M., Rosadini, G. and Rossi, G.F. (1965): Excitability cycle of the visual cortex during sleep and wakefulness. Electroenceph. Clin. Neurophysiol. 19:276-283.

Vernon Rowland

Rowland, V. (1957): Differential electroencephalographic response to conditioned auditory stimuli in arousal from sleep. Electroenceph. Clin. Neurophysiol. 9:985-994.

Rowland, V. (1959): Conditioning and brain waves. Sci. Amer. 201:89-96.

Gluck, H. and Rowland, V. (1959): Defensive conditioning of electroencephalographic arousal with delayed and differ-

entiated auditory stimuli. Electroenceph. Clin. Neurophysiol. 11:485-496.

Rowland, V. and Gluck, H. (1960): Electrographic arousal and its inhibition as studied by auditory conditioning. In: Recent Advances in Biological Psychiatry. Wortis, J., ed. New York: Grune & Stratton, Pp. 96-105.

Rowland, V. (1961): Electrographic responses in sleeping conditioned animals. In: CIBA Foundation Symposium on the Nature of Sleep. Wolstenholme, G.E.W. and O'Connor, M., eds. London: Churchill, Pp. 284-306.

Harold L. Williams

Williams, H.L., Lubin, A. and Goodnow, J.J. (1959): Impaired performance with acute sleep loss. Psychol. Monogr. 73(14): 1-26.

Williams, H.L., Granda, A.M., Jones, R.C., Lubin, A. and Armington, J.C. (1962): EEG frequency and finger pulse volume as predictors of reaction time during sleep loss. Electroenceph. Clin. Neurophysiol. 14:64-70.

Williams, H.L., Morris, G.O. and Lubin, A. (1962): Illusions, hallucinations and sleep loss. In: Hallucinations. West, L.J., ed. New York: Grune & Stratton, Pp. 158-165.

Loveland, N.T. and Williams, H.L. (1963): Adding, sleep loss, and body temperature. Percept. Motor Skills 16:923-929.

Williams, H.L., Hammack, J.T., Daly, R.L., Dement, W. and Lubin, A. (1964): Responses to auditory stimulation, sleep loss and the EEG stages of sleep. Electroenceph. Clin. Neurophysiol. 16:269-279.

Williams, H.L., Morlock, H.C. and Morlock, J.V. (1966): Instrumental behavior during sleep. Psychophysiology 2:208-216.

* * *